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[Continued on next page]

(54) Title: NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE AND ACTIVITY IN MAMMALS

Percent Change in Plasma Proteins 12 hr post 2 nd dose /pre-dose													
				SU6668.004 BID (Tablets) Plasma/Pharmacokinetics for Day 1									
Pt #	SU6668 Dose (mg/m ²)	cancer type	gender	SU6668 Cmax (ug/mL)	Tmax hrs	Exposure >2.3 ug/mL (hrs)	AUC ug*hr/mL	PAI-1	VEGF	MMP-9	TIMP-1	TF	
28	400	prostate	M	13.0	15.0	21.3	164.3	297		46	27	21	
32	300	ovarian	F	12.9	2.0	11.8	85.7	19	94	-45	-3	19	
34	300	laryngeal	M	11.6	3.5	10.7	136.4	63	-1	156	-2	5	
17	200	colon	F	11.5	2.0	11.0	66.1	221			105	24	
25	300	colon	M	11.0	2.0	13.4	75.5	7	-27	184	69	22	
27	400	colon	M	10.3	6.0	9.1	71.2	40	10	-15	-5	32	
19	200	leiomyosarcoma	F	9.5	4.0	12.8	80.2	104	95	36	0.2	12	
23	300	renal	F	9.3	2.0	8.0	53.5	59	36	79	9	9	
16	200	thyroid	F	9.3	2.0	7.3	55.7	263		409	43	37	
24	300	leiomyosarcoma	F	8.2	4.0	16.4	71.2	62	9	18	27	39	
30	300	testicular	M	7.9	1.0	2.1	32.9	52	82	-66	13	1	
33	300	testicular	M	7.5	5.0	10.4	43.2	20	121	305	99	212	
31	300	hepatocellular	F	6.9	4.0	7.3	55.8	29	100	1	0	227	
20	200	prostate	M	5.9	2.5	10.9	68.5	47	181	48	40	38	
26	300	prostate	M	5.6	2.0	8.2	57.0	2	50	38	21	8	
15	200	breast	F	5.3	2.0	4.8	44.0	95	14	1	14	9	
35	300	thyroid	M	4.3	1.5	16.1	97.5	65	24	19	64	65	
22	300	colon	M	2.5	4.0	0.5	20.8	14	23	29	3	5	
	>500%												
	29 to 500 %												
	-66 to 28%												

(57) Abstract: The present invention describes novel methods that measure in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one biomarker in a mammal exposed to a test compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine kinase activity.

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[0001] This application claims benefit of priority from U.S. provisional application Ser. Nos 60/380,872, filed May 17, 2002, 60/448,922, filed February 24, 2003, and 60/448,874, filed February 24, 2003, all of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] A biomarker is a molecular marker of a biological event or phenomenon in a organism. Changes in the level of certain biomakers indicate a biological response to a chemical compound in an organism. Biological responses include events at the molecular, cellular or whole organism level. Changes in biomarker levels can be measured and used to indicate whether or not a particular effect has been achieved in the organism. Changes in biomarker levels can indicate that an organism has been exposed to a particular compound. Changes in biomarker levels also can indicate whether an organism is experiencing or will experience a therapeutic effect or even a toxic event in response to a compound.

SUMMARY OF INVENTION

[0003] The present invention relates to novel methods comprising measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. In the novel methods, the level of at least one biomarker in a mammal exposed to a compound is compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound.

[0004] The invention includes methods for determining whether a test compound inhibits the activity of a protein tyrosine kinase. The invention further relates to methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also discloses methods for determining if a mammal is responsive to the administration of a compound that inhibits tyrosine kinase activity. In addition, the invention relates to methods for identifying mammals that will respond therapeutically to a compound that inhibits VEGFR and/or PDGFR tyrosine kinases. The invention further discloses methods for testing or predicting, as well as kits for determining, whether a mammal will respond therapeutically to a compound that inhibits tyrosine kinase activity. The invention also relates to methods for testing or predicting whether a mammal

will experience an adverse event, such as fatigue, in response to a method of treatment comprising administering a compound that inhibits tyrosine kinase activity.

[0005]

BRIEF DESCRIPTION OF THE FIGURES

[0006] Figure 1 shows the levels of various plasma proteins in plasma from human patients, measured by ELISA, before and 24 hours after the first dose of Compound A (SU6668).

[0007] Figure 2 shows the abundance of a protein (spot #5) in patient plasma, measured by 2D polyacrylamide gel analysis, before and 4 hours after the first dose of Compound A (SU6668).

[0008] Figure 3 shows the identification by mass spectrometry analysis of spot #5 from the 2D gel analysis of patient plasma analyzed in Figure 2.

[0009] Figure 4A shows the change in level of various RNA transcripts, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis. Figure 4B shows the change in the level of vinculin RNA, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis.

[0010] Figure 5 shows the levels of various RNA transcripts, in patient blood samples, on treatment day 28 (27 days after the first dose of Compound A) versus the levels on treatment day 0 (before treatment with Compound A). Numbers shown indicate increase and/or decrease relative to baseline on day 0. No significant change is shown as ~1. Levels decreased are less than 1 and levels increased are greater than 1.

[0011] Figure 6 shows the differential expression of candidate biomarker transcripts in patient PBMC at day 56 relative to day 1 of therapy. The diagram is a depiction of the Affymetrix Difference Calls assigned to each day 56:day 1 expression comparison among the patient sample pairs analyzed via GeneChip hybridization analysis. Letters within blocks represent the Difference Call assigned to each relative expression comparison. The abbreviations are: I = Increase, MI = Marginally Increased, NC = Not Changed; MD = Marginally Decreased; D = Decreased. Cases in which an Increased or Marginally Increased call is assigned to a day 56:day 1 comparison are shaded in gray. Each column represents a different patient. Column headings in each grid represent patient response assessed at the end

of first treatment cycle: PR = partial response, CR = complete response, PD = progressive disease.

[0012] Figures 7A and 7B show the percentage of patients with increased expression of biomarker transcripts following treatment with Compound B (SU5416). Differential expression of six transcripts as measured by microarray and quantitative RT-PCR is presented. The percentage of cases in 5-FU/LV (control) and 5-FU/LV + SU5416 trial arms with increased expression (at predose day 56 relative to predose day 1) of each transcript is displayed. Figure 7A shows the results of the Affymetrix analysis and Figure 7B shows the results from SYBR Green RT-PCR. For the SYBR Green data, an increased is defined as relative expression value of 2-fold or greater. A total of 31 sample pairs were used in RT-PCR analysis; 18 were from SU5416 arm (5 PR, 1 CR, 11 PD and 1 SD response at end of cycle 1), and 13 were from the control arm (9 PR, 3 PD and 1 SD).

[0013] Figure 8 shows the percentage of patients with increased expression of four biomarker transcripts, following treatment with Compound B (SU5416). Differential expression of four transcripts as measured by quantitative RT-PCT is presented. Percentage of cases in CPT-11/5-FU/LV (control) and CPT-11/5-FU/LV + SU5416 trial arms with increased expression (at predose day 42 relative to predose day 1) of four candidate biomarker transcripts in a second SU5416 Phase III clinical trial is displayed. The convention is the same as in panel B in Figure 7. A total of 36 sample pairs was included in this analysis; 18 from the Compound B arm and 18 from the control arm (8 PR and 10 SD responses at end of cycle 1 in each group).

[0014] Figure 9 shows hierarchical clustering of relative expression ratios for four biomarker transcripts. This mosaic depicts association between patient samples and relative expression of the four potential biomarker transcripts. Natural log-transformed SYBR Green RT-PCR ratio data (relative expression of day 56:day 1) were used in analysis. In the color scheme, higher ratios are indicated in red, lower ones in green (scale ranges from -4 to +4). Results from individual patients are oriented as rows and transcripts are oriented as columns. Red bars on the right side of the map indicate cases from the SU4316 arm. The hierarchical clustering method is average linkage and the distance metric is Euclidean.

[0015] Figure 10 shows PAI-1 levels on day 1 and day 56 in patient plasma samples. MR = minor response (cycle 1); PR = partial response (cycle 1); PD = progressive disease (cycle 1)

[0016] Figure 11 shows the mRNA and protein sequences for lactoferrin (SEQ ID NOS 68-69, respectively), lipocalin-2 (SEQ ID NOS 70-71 and 180, respectively), MMP9 (SEQ ID NOS 72 & 66, respectively), and CD24 (SEQ ID NO: 73-74, respectively).

[0017] Figure 12 shows mRNA and protein sequences for eucaryotic initiation factor 4A11 (SEQ ID NOS 75-76, respectively), human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792) (SEQ ID NOS 77-78, respectively), Homo sapiens thymosin beta-10 (SEQ ID NOS 79-80, respectively), Homo sapiens hnRNPcore protein A1 (SEQ ID NOS 81-82, respectively), human leucocyte antigen (CD37) (SEQ ID NOS 83-84, respectively), human MHC class II HLA-DR beta-1 (SEQ ID NOS 85-86, respectively), Homo sapiens translation initiation factor eIF3 p66 subunit (SEQ ID NOS 87-88, respectively), Homo sapiens nm23-H2 gene (SEQ ID NOS 89-90, respectively), human acidic ribosomal phosphoprotein P0 (SEQ ID NOS 91-92, respectively), human cyclophilin (SEQ ID NOS 93-94, respectively), Genbank Accession No. AI541256 (cDNA) (SEQ ID NO: 95), human T-cell receptor active beta chain (SEQ ID NOS 96-97, respectively), human MHC class II lymphocyte antigen (HLA-DP) beta chain (SEQ ID NOS 98-99, respectively), human KIAA0195 (SEQ ID NOS 100-101, respectively), Homo sapiens MAP kinase kinase 3 (MKK3) (SEQ ID NOS 102-103, respectively), human beta-tubulin class III isotype (beta-3) (SEQ ID NOS 104-105, respectively), human tropomyosin (SEQ ID NOS 106-107, respectively), 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C (SEQ ID NOS 108-109, respectively), human MLC emb gene for embryonic myosin alkaline light chain (SEQ ID NOS 110-111, respectively), Homo sapiens glyoxalase II (SEQ ID NOS 112-113, respectively), Homo sapiens trans-golgi network glycoprotein 48 (SEQ ID NOS 114-115, respectively), histone H2B (SEQ ID NOS 116-117, respectively), human RLIP76 protein (SEQ ID NOS 118-119, respectively), Genbank Accession No. W26677 (human retina cDNA) (SEQ ID NO: 120), human PMI gene for a putative receptor protein (SEQ ID NOS 121-122, respectively), human DNA-binding protein A (dbpA) (SEQ ID NOS 123-124, respectively), human ITIH4 (SEQ ID NOS 125-126, respectively), IL-8 (SEQ ID NOS 182-183, respectively) and C-reactive protein (SEQ ID NOS 184-185, respectively).

[0018] Figure 13 shows the changes in VEGF plasma levels, as measured by ELISA, in patients receiving a malate salt of Compound 1 in Trial C.

[0019] Figure 14 shows by hybrid ELISA that VEGF/PLGF heterodimers are detected in plasma of cancer patients and are induced in patients after treatment with a malate salt of Compound 1 in Trial C. The hybrid ELISA assay demonstrates that levels of

heterodimers are increased in 3 of 3 patients tested, and follow a pattern of induction similar to that seen for VEGF and PLGF.

[0020] Figure 15 shows that plasma levels of soluble VEGFR2 decrease in patients in Trial D following treatment with a malate salt of Compound 1 in a dose-dependent manner.

[0021] Figure 16 shows that the decrease in sVEGFR2 following treatment with Compound 1 or malate salt thereof correlates with AUC values (end of C1 dosing, all trials). The scatter graph plots sVEGFR2 fold change (end of cycle 1 dosing over baseline) against AUC values from end of cycle 1 dosing. Results from the first 44 patients (representing 4 trials) are included.

[0022] Figure 17 shows that chemokine MIG is induced in patients during treatment with a malate salt of Compound 1. MIG is a biomarker that also correlates with tumor responses as measured by ¹⁸FDG-PET imaging. Results are from Trial C.

[0023] Figure 18 discloses the amino acid sequence of human vascular endothelial growth factor (VEGF) (SEQ ID NO: 127).

[0024] Figure 19 discloses the amino acid sequence of human placenta growth factor (PLGF) (SEQ ID NO: 128).

[0025] Figure 20 discloses the amino acid sequence of human vascular endothelial growth factor receptor 2 (VEGFR2) (SEQ ID NO: 129).

[0026] Figure 21 discloses the amino acid sequence of human Monokine Induced by Interferon-Gamma (MIG) (SEQ ID NO: 55).

[0027] Figure 22 discloses the amino acid sequence of human interferon-inducible cytokine IP-10 (SEQ ID NO: 130).

[0028] Figure 23 discloses the amino acid sequence of human Interferon-inducible T-cell alpha chemoattractant (I-TAC) (SEQ ID NO: 131).

[0029] Figure 24 shows cDNA or mRNA sequences for human vinculin (SEQ ID NOS 132 & 181, respectively), basic transcription factor 3 homologue (SEQ ID NO: 133), human c-jun proto oncogene (SEQ ID NO: 134), human c-fos proto-oncogen (SEQ ID NO: 135), Homo sapien PTP-nonreceptor type 2 (SEQ ID NO: 136), human cdc2-related protein kinase (SEQ ID NO: 137), human cyclin C (SEQ ID NO: 138), human DNA polymerase-gamma (SEQ ID NO: 139), protein kinase C-alpha (SEQ ID NO: 140), lipocortin II/annexin

A2 (SEQ ID NO: 141), histone H2B member R (SEQ ID NO: 142), Homo sapien amphiregulin (SEQ ID NO: 143), human basic transcription factor 3 (SEQ ID NO: 144), Homo sapien phosphoinositide-3-kinase p110 subunit (SEQ ID NO: 145), human gelsolin (SEQ ID NO: 146), Homo sapien Cyclin D2 (SEQ ID NO: 147), ephrin receptor (EphB4) (SEQ ID NO: 148), human Hanukah factor/granzyme A (SEQ ID NO: 149), von Hippel-Lindau (VHL) tumor suppressor (SEQ ID NO: 150), human mRNA for OB-cadherin-1 (SEQ ID NO: 151), human mRNA for OB-cadherin-2 (SEQ ID NO: 152), phosphoinositol 3-phosphate-binding protein-3 (PEPP3) (SEQ ID NO: 153), human phosphoinositol 3-kinase p85 subunit (SEQ ID NO: 154), human mucin 1 (SEQ ID NO: 155), ErbB3/HER3 receptor tyrosine kinase (SEQ ID NO: 156), and Homo sapien gene for hepatitis C-associated microtubular aggregate protein p44 (nine exons) (SEQ ID NOS 157-164, respectively).

[0030] Figure 25 shows that FLT3 ligand (FL) is induced in patients during treatment with Compound 1.

[0031] Figure 26 demonstrates that interleukin-6 (IL-6) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in IL-6 plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0032] Figure 27 demonstrates that C-reactive protein (CRP) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in CRP plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0033] Figure 28 shows that a higher baseline value of CRP in patients with GIST correlates with progressive disease, in Trial D.

[0034] Figure 29 shows that protein expression of OB-cadherin 1 (cadherin 11) is up-regulated in Colo205 xenograph tumors after exposure to Compound 1 for 24 or 48 hours.

BRIEF DESCRIPTION OF THE TABLES

[0035] Tables 1-22 appear following the Examples disclosed in this application, and specifically after Section K.

[0036] Table 1 shows Compound B (SU5416) PBMC sample processing history for Trial A.

[0037] Table 2 shows a list of biomarker transcripts as detected in Affymetrix analysis.

[0038] Table 3 shows primer sequences used in RT-PCR validation analysis.

[0039] Table 4 shows a Mann-Whitney U Test comparison of expression fold change data from Compound B and control arms (Trial A). This statistical analysis was performed to assess the significance of differences in expression change ratios (day 56 vs day 1) between the Compound B and control arms. Separate comparisons were performed of expression change values from Affymetrix analysis and from SYBR Green RT-PCR validation experiments. P-values ≤ 0.05 were considered statistically significant.

[0040] Table 5 shows the Mann-Whitney U Test of Compound B expression data in Trial B.

[0041] Table 6 shows a summary of class prediction results for pooled data (3 gene predictor set).

[0042] Table 7 shows changes in plasma levels of PLGF in patients in Trial C receiving daily treatment with a malate salt of Compound 1.

[0043] Table 8 shows changes in plasma levels of MIG, IP-10, and I-TAC in patients receiving treatment with Compound 1 or a malate salt thereof. Levels of IP-10 and I-TAC at end cycle 1 dosing are estimated values in some cases (>500), as the amount of IP-10 or I-TAC in these samples was higher than the highest standard provided for standard curve generation. All patients represented in this table are from Trial C, except for patient 11 from Trial B and patient 9 from Trial A. Patients in Trial C received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0044] Table 9 shows changes in PLGF and/or sVEGFR2 plasma levels in cancer patients after receiving treatment with Compound 1 or a malate salt thereof. For PLGF, *italics text* indicates a fold-change of 3-fold or greater, end of cycle 1 dosing relative to day 1. For sVEGFR2, *italics text* indicates a decrease of 30% or more, end of cycle 1 dosing relative to day 1. Patients in Trials C and D received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0045] Table 10 shows an increase in MIG plasma levels in cancer patients after receiving treatment with Compound 1 or malate salt thereof. As with Table 2, results are from Trial C except for patient 11 from Trial B and patient 9 from Trial A..

[0046] Table 11A shows the change in levels of various mRNA transcripts isolated from Colo205 xenograft tumors, as measured by DNA Array analysis, before exposure to Compound 1, and 6 hours and 24 hours after exposure to the first dose of Compound 1.

[0047] Table 11B shows the change in levels of various mRNA transcripts isolated from SF767 xenograft tumors, measured by DNA Array analysis, before exposure to Compound 1, and 4 hours and 24 hours after exposure to the first dose of Compound 1.

[0048] Table 12 shows the change in the levels of protein expression and/or mRNA transcript abundance in Colo205 xenograft tumors, as measured by Taqman Real Time PCR, before exposure to Compound 1, and at 6 hours versus 24 hours after exposure to the first dose of Compound 1. The following transcripts were measured: Amphiregulin, Cdc2-related protein kinase, phosphoinositol 3-kinase, p110 subunit, cyclin C, OB-Cadherin1, OB-Cadherin2, p85 subunit, Mucin 1, von Hippel-Lindau (VHL) tumor suppressor, ephrin receptor (EphB4), and Gelsolin.

[0049] Table 13 shows the forward and reverse primer and probe sequences used in the TaqMan Real Time PCR Analysis of Colo205 xenograft tumor samples.

[0050] Table 14 lists three sets of 2D gels used in MALDI-TOF-MS and MALDI-MS/MS analysis.

[0051] Table 15 shows the quantification of Spot #1202 from 2D gel analysis. 2D gel analysis was performed on samples isolated from HUVECs that were stimulated with VEGF after pre-treatment with Compound 1 or vehicle control (DMSO).

[0052] Table 16 shows definitive identification of Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-TOF-MS analysis.

[0053] Table 17 identifies Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-MS/MS analysis.

[0054] Table 18 shows quantitative ELISA analysis of pro-MMP1 levels in HUVEC conditioned media, after stimulation of HUVEC cells with VEGF after pre-treatment with Compound 1 at 10 nM, 100 nM or 1 μ M concentrations, or vehicle control (DMSO).

[0055] Table 19 shows an increase pro-MMP1 levels in patient plasma after treatment with Compound 1. Results are from Study B.

[0056] Table 20 lists the analytes measured using Array 1.1 and Array 2.1 in an antibody chip microassay analysis.

[0057] Table 21 lists 23 biomarkers that show changes in plasma levels following treatment with Compound 1. An up arrow, down arrow or (-) denote relative increase, decrease or no change in detected level respectively, in samples for patients 1, 2 and 3. The

accession numbers for markers, not previously described herein, are as follows: ENA-78 (epithelial derived neutrophil activating protein 78) (SEQ ID NO: 48), P42830; MPIF-1 (myeloid progenitor inhibitory factor 1) (SEQ ID NO: 49), P55773; GCP-2 (gamma tubulin complex component 2) (SEQ ID NO: 50), Q9BSJ2; Amphiregulin (Amphireg) (SEQ ID NO: 51), AAA51781; IL-1 α (interleukin-1 alpha) (SEQ ID NO: 52), NP 000566 for preprotein; IL-1 β (interleukin-1 beta) (SEQ ID NO: 53), NP000567 for preprotein; IL-2 (interleukin-2) (SEQ ID NO: 54), NP000577 for preprotein; MIG (mitogen inducible gene) (SEQ ID NO: 55), NP 061821; NT4 (neurotrophin 4/neurotrophic factor 5) (SEQ ID NO: 56), NP 006170; IGFBP-1 (insulin-like growth factor binding factor-1) (SEQ ID NO: 57), NP 000587; GRO- β (SEQ ID NO: 58), AAA63183; TNFR1 (tumor necrosis factor receptor 1) (SEQ ID NO: 59), P19438; FLT3 ligand (fms-like tyrosine kinase ligand/Flk 2 ligand) (SEQ ID NO: 60), I38440; IL-6 (interleukin-6) (SEQ ID NO: 61), NP-000591; MCP-1 (monocyte chemoattractant protein 1) (SEQ ID NO: 62), P13500; TNF α (tumor necrosis factor alpha) (SEQ ID NO: 63), NP 000585; TARC (thymus and activation regulated chemokine) (SEQ ID NO: 64), Q92583; MMP7 (SEQ ID NO: 65), NP 002414 for preprotein; MMP9 (SEQ ID NO: 66), NP 004985 for preprotein; and leptin (SEQ ID NO: 67), NP000221 for preprotein. Note that accession numbers and SEQ ID NOs in this specification are used to identify cDNAs, mRNAs or proteins of interest, rather limit the biomarkers to specific sequences.

[0058] Table 22 shows the relative fold change of six plasma biomarkers in three patients (denoted 1, 2 and 3) following Compound 1 treatment relative to predose, as measured by two methods: ELISA; and antibody chip technology (MSI).

DETAILED DESCRIPTION OF THE INVENTION

[0059] The present invention relates to novel methods for determining whether a test compound inhibits tyrosine kinase activity and novel methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also relates to novel methods for determining whether a mammal is experiencing or will experience a particular biological phenomenon, such as a therapeutic effect, "responding" (as defined herein), or an adverse event, in response to a compound that inhibit tyrosine kinase activity.

[0060] The novel methods comprise measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one

biomarker in the mammal exposed with a test compound, as compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The tyrosine kinases of the novel methods include, but are not limited to, those selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor.

[0061] In certain embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone, as described herein, and also in U.S. Serial No. 10/281,266. In other embodiments, the tyrosine kinase inhibitor comprises compounds described in U.S. Ser. No. 09/783,264, WO 01/60814, U.S. Ser. No. 10/076,140, U.S. Ser. No. 10/281,266, U.S. Ser. No. 10/281,985, U.S. Ser. No. 10/237,966 (now a U.S. provisional application), as well as a U.S. provisional application Ser. No. 60/448,861, filed February 24, 2003 (entitled "Treatment of excessive osteolysis with indolinone compounds"), all of which are hereby incorporated by reference.

[0062] Identification of biomarkers that provide rapid and accessible readouts of efficacy, drug exposure, or clinical response is increasingly important in the clinical development of drug candidates. Embodiments of the invention include measuring changes in the expression levels of secreted proteins, or plasma markers, which represent one category of biomarker. In one embodiment, plasma samples, which represent a readily accessible source of material, serve as a surrogate tissue for biomarker analysis.

A. Definitions

[0063] Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below.

[0064] "Test compound" refers to any pharmaceutical composition that inhibits or modulates a protein tyrosine kinase.

[0065] "Tyrosine kinase modulator" or "tyrosine kinase inhibitor" refers to any chemical composition that modulates, affects, alters, inhibits or reduces the enzymatic activity or tyrosine phosphorylation action of a tyrosine kinase.

B. Biomarkers Modulated in Mammals Exposed to Tyrosine Kinase Inhibitors

[0066] In one embodiment, the invention includes a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

[0067] Alternatively, a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

[0068] In an other embodiment, the invention includes a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated

microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

[0069] Alternatively, a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative

receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPlF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

[0070] In an other embodiment, the invention includes a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0071] Alternatively, a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase

precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0072] In another embodiment, the invention includes a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1,

GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

[0073] Alternatively, a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic

transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

[0074] The term “responding” encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect or an adverse event), in a mammal.

[0075] In another embodiment, the invention includes a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation

initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0076] In another embodiment, the invention includes a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in a same type of mammal without cancer the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the

mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0077] As used throughout the specification, the term “respond therapeutically” refers to the alleviation or abrogation of a disease, such as cancer. This term means that the life expectancy of an individual affected with the disease will be increased or that one or more of the symptoms of the disease will be reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known in the art, such as PET imaging.

[0078] In another embodiment, the mammal is a human. In other embodiments, the mammal is a rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate, or monkey.

[0079] In other embodiments, any of the preceding methods is an in vitro method, and the protein and/or mRNA biomarker is measured in at least one mammalian biological tissue. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological fluid, including but not limited to whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological tissue including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

[0080] In yet other embodiments, the methods of the invention are carried out on mammals who have cancer. The cancer can be, for example, but is not limited to, prostate cancer, colorectal cancer (CRC), thyroid cancer, an advanced solid malignancy, pancreatic cancer, breast cancer, parotid cancer, synovial cell cancer or sarcoma, gastrointestinal stromal tumor (GIST), laryngeal cancer, testicular cancer, leiomyosarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, ovary cancer, lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvis sarcoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, neuroendocrine cancer, bronchial adenocarcinoma, head and neck cancer and/or thymic cancer.

[0081] In other embodiments, any of the preceding methods also comprise a step wherein the mammal is also exposed to a cancer chemotherapeutic agent before, during and/or after exposure to the compound that inhibits tyrosine kinase activity.

[0082] Other embodiments also include any of the preceding methods, wherein the “difference” refers to an increase in the level of at least one of the following protein(s) and/or

mRNA transcript(s): PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2B, human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ephrin receptor EphB4, OB-cadherin 1, phosphoinositol 3-kinase p85 subunit, mucin 1 and gelsolin, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0083] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of prostate cancer, colon cancer, thyroid cancer and an advance solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of VEGF protein and/or mRNA transcript as measured before exposure to the compound.

[0084] Other embodiments also include any of the proceeding methods wherein the mammal has colon or colorectal cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, MMP-9, lactoferrin, lipocalin-2, and/or CD24 antigen protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0085] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of synovial sarcoma, rectal cancer, gall-bladder cancer,

hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvis sarcoma, parotid cancer, uterine cancer, pelvic angiosarcoma, colorectal cancer and gastrointestinal stromal tumor (GIST), and wherein the “difference” refers to an increase in the level of at least one of VEGF, PLGF and VEGF/PLGF heterodimers protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0086] Other embodiments also include any of the preceding methods wherein the mammal has an advanced solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF and/or MMP-9 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0087] Other embodiments also include any of the preceding methods wherein the mammal has at least one of pancreatic cancer, synovial sarcoma, colon cancer, non-small cell lung cancer (NSCLC), rectal cancer, pelvis sarcoma, and sarcoma and/or bronchial adenocarcinoma, and wherein the “difference” refers to an increase in the level of at least one of MIG, IP-10 and I-TAC protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0088] Other embodiments also include any of the preceding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2b and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0089] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to an increase in the level of at least one of eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0090] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to an increase in the level of at least one of human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0091] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0092] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to an increase in the level of at least one of Homo sapiens thymosin beta-10 gene, Homo sapiens MAP kinase kinase 3

(MKK3) and histone H2B member R protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0093] Other embodiments also include any of the proceeding methods wherein the mammal has synovial cell cancer, and wherein the “difference” refers to an increase in the level of human RLIP76 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of human RLIP76 protein and/or mRNA transcript as measured before exposure to the compound.

[0094] Other embodiments also include any of the proceeding methods, wherein the “difference” refers to a decrease in the level of at least one of the following protein(s) and/or mRNA transcript(s): ITIH4, PAI-1, soluble VEGF receptor 2 (sVEGFR2), Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78, MPIF-1, MMP7, MIG, cdc2 related protein kinase, and phosphoinositol 3-kinase p110 subunit, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0095] Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of breast cancer, prostate cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of ITIH4 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of ITIH4 protein and/or mRNA transcript as measured before exposure to the compound.

[0096] Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of synovial sarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, melanoma, colon cancer, renal cell carcinoma, non-small cell lung cancer (NSCLC), sarcoma, retroperitoneal sarcoma, pelvis sarcoma, squamous cell carcinoma parotid cancer, bronchial adenocarcinoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, colorectal cancer (CRC), neuroendocrine cancer, gastrointestinal stromal tumor (GIST), head and neck cancer, thymic cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of sVEGFR2 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of sVEGFR2 protein and/or mRNA transcript as measured before exposure to the compound.

[0097] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to a decrease in the level of at least one of Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human beta-tubulin class III isotype (beta-3), and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0098] Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0099] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo

sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0100] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to a decrease in the level of at least one of human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0101] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, Homo sapiens trans-golgi network glycoprotein 48, histone H2B and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0102] In another embodiment, the invention also includes a kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic

ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

[0103] In another embodiment, the invention also includes the preceding kit, wherein the instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens

cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

[0104] wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

[0105] In another embodiment, the invention also includes a method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

[0106] As used in the specification, the term “adverse event” refers to a physiological effect in a mammal, such as fatigue or other side effect, that is severe enough to warrant altering, reducing or eliminating the mammal’s exposure to a particular tyrosine kinase inhibitor. Exposure or administration can be altered, reduced or eliminated in terms of the amount or dosage of the tyrosine kinase inhibitor, as well as length of time and/or frequency of exposure. A determination as to whether a particular physiological effect is severe enough to be considered “an adverse event” falls within the judgment of those skilled in the art, such as a laboratory scientist, veterinarian or medical practitioner.

C. Further Embodiments of the Novel Methods

1. Measurement of Protein and mRNA

[0107] In other embodiments, the novel methods of Section B are carried out so that the step where the mammal is exposed to test compound includes administration of at least one dose of test compound, or at least two doses, or at least 5 doses or at least 10 doses, up to at least 55 or 56 doses. In certain embodiments, these doses are administered during a period of 4 hours, 6 hours, or 24 hours to about 100 days. In further embodiments, the doses are administered over a period of 24 hours, 2 days, or 28 days. In other embodiments, two doses are administered per every 24 hours, and in other embodiments, the doses are administered about every 12 hours. It will be understood by those of skill in the art that the administration of test compound, according to the exposure steps of the methods of Section B, can be varied to suit individual needs of the mammal being treated, the compound being administered, the method of administration and the disease being treated. For example, in a typical dosing regimen, the patient receives one dose per day of test compound, for a number of days, such

as about 28 or about 56 days. In other dosing regimens, the test compound is administered about once per day, twice per week, or once per week.

[0108] The measurement of protein and/or RNA, following the exposure step in the methods of Section B, can be carried out on a sample from the mammal taken about 4 or 6 hours following the first dose (exposure) of the mammal to test compound. In other embodiments, this measurement is carried out on a sample taken 12 hours, 1 day, 2 days, up to about 100 days, after the first dose (exposure) of the mammal to test compound. In other embodiments, the protein and/or mRNA measurements are taken from samples from the mammals 4 or 6 hours after the first dose of test compound or 24 hours after the first dose of test compound, or 15 or 28 days after the first dose of test compound. Typically, dosing of test compound will be periodic between the first and last dose of test compound that precedes the sample taken for measurement of biomarker protein and/or mRNA. For example, the test compound is administered once a day, every day for 28 days. Typically, the mammal sample taken (for measurement of biomarker protein and/or mRNA) will be taken shortly following the most recent dose of test compound, for example within 24 of the most recent dose of test compound.

[0109] In other embodiments, the methods of Section B are carried out so that the measurement of protein and/or mRNA is carried out on a mammalian tissue selected from biological fluids, including but not limited to the group of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, and other tissues including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue, bone marrow.

[0110] In other embodiments, the methods of Section B are carried out on a mammal that is further exposed to other chemotherapeutic agents, including but not limited to 5-fluoro-uracil (5-FU), leucovorin, CPT11, aromasin, taxol, paclitaxel, other “standard of care” agents used in patients, COX-2 inhibitors (such as celecoxib), and other tyrosine kinase inhibitors. Such exposure to a cancer chemotherapeutic agent can be before, during and/or after exposure to test compound.

[0111] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least

25%. In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 2-, 3-, 5-, 10-, 15- or 24-fold. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5-, 4.0-, 4.2-, 4.5-, 5.0-, 5.5-, 6.0-, 6.1-, 6.5-, 7.0-, 7.3-, 10.0-, 15.0-, 19.0- or 24-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 1.7- or 2.0-fold.

[0112] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 25%. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5- or 3.7-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 1.7- or 2.0-fold.

[0113] To quantify the protein and/or mRNA measured in the novel methods of Section B, methods well known to the skilled artisan are used. For example, quantification of protein can be carried out using methods such as ELISA, 2-dimensional SDS PAGE, Western Blot, immunoprecipitation, immunohistochemistry, fluorescence activated cell sorting (FACS), flow cytometry. Quantification of mRNA is measured using methods such as PCR, array hybridization, Northern blot, in-situ hybridization, dot-blot, Taqman, RNase protection assay.

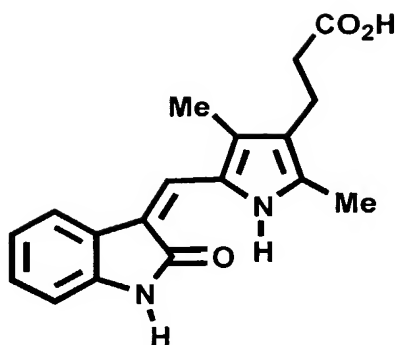
[0114] In further embodiments of the invention, the methods of Section B are carried out so that the level of at least two, or at least three, or at least four, or at least five, or at least 6, or at least seven or at least eight, or at least nine, up to 87 of the biomarkers are measured in a mammal. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 66 biomarkers of Section B that are increased upon exposure of a mammal to a compound that inhibits tyrosine kinase. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 39 biomarkers of Section B that are decreased upon exposure of a mammal to a compound that inhibits tyrosine kinase.

2. Tyrosine Kinase and Inhibitors of Tyrosine Kinase

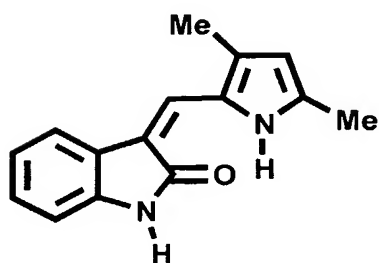
[0115] In certain embodiments, the tyrosine kinases of the novel methods are selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor. See, for example, U.S. Pat. No. 6,177,401 (Flk-1), WO 01/45689 (c-kit), GenBank Accession No. NM 002609 (PDGFR-beta), GenBank Accession No. NM 006206 (PDGFR-alpha), GenBank Accession No. NM 023109 (FGFR-1), GenBank Accession No. NM 023028 (FGFR-2) and GenBank Accession No. NP_005202 (c-fms/CSF-1 receptor).

[0116] FLT3 (fms like tyrosine kinase 3) is a member of the class III receptor tyrosine kinases. Those of skill in the art will recognize that FLT3 has also been called "flk2" in the scientific literature. "FLT3" as used herein, refers to a polypeptide having, for example, the sequence set forth in accession number gi|4758396|ref|NP_004110.1| fms-related tyrosine kinase 3 [Homo sapiens], or gi|544320|sp|P36888|FLT3_HUMAN FL CYTOKINE RECEPTOR PRECURSOR (TYROSINE-PROTEIN KINASE RECEPTOR FLT3) (STEM CELL TYROSINE KINASE 1) (STK-1) (CD135 ANTIGEN), or gi|409573|gb|AAA18947.1| (U02687) serine/threonine protein kinase [Homo sapiens]. Corresponding mRNA accessions for the first two sequences are gi|4758395|ref|NM_004119.1| Homo sapiens fms-related tyrosine kinase 3 (FLT3), mRNA gi|406322|emb|Z26652.1|HSFLT3RTK H.sapiens FLT3 mRNA for FLT3 receptor tyrosine kinase.

[0117] In other embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone compound. In another embodiment, the test compound is a compound of Formula I. These, and other exemplary tyrosine kinase inhibitors, are shown below. The skilled artisan will recognize that the novel methods of the invention can be used to test any tyrosine kinase inhibitor, in addition to those listed below.



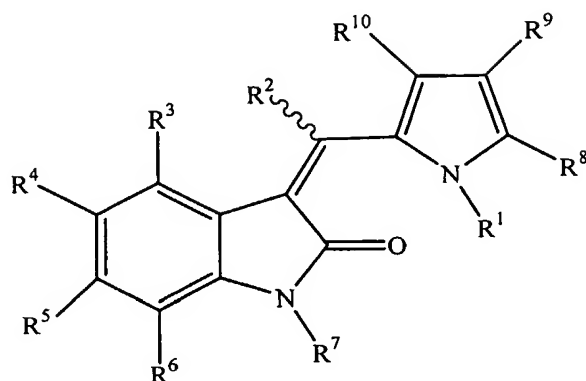
[0118] Compound A (SU6668): 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.



[0119] Compound B (SU5416): 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one.

[0120]

A pyrrole substituted 2-indolinone having the formula:



wherein:

R^1 , R^2 and R^7 are hydrogen;

R^3 , R^4 , R^5 , and R^6 are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

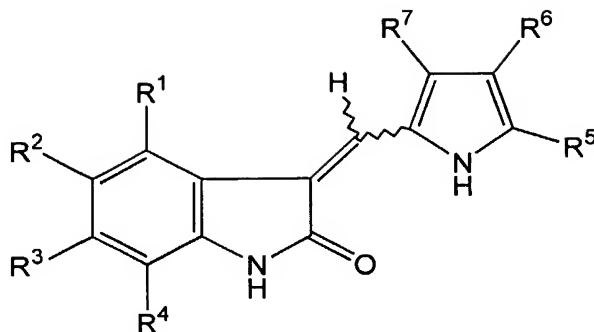
R^8 is unsubstituted lower alkyl;

R^9 is $-(CH_2)(CH_2)C(=O)OH$; and

R^{10} is unsubstituted lower alkyl.

[0121]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_tR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14}$, $-S(O)_2NR^{13}R^{14}$,

$-NR^{13}C(O)R^{14}$,

$-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and

heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5 , R^6 or R^7 must be $-C(O)R^{10}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl and aryl;

R^{10} is selected from the group consisting of hydroxy, alkoxy, aryloxy, - $N(R^{11})(CH_2)_nR^{12}$, and $-NR^{13}R^{14}$;

R^{11} is selected from the group consisting of hydrogen and alkyl;

R^{12} is selected from the group consisting of $-NR^{13}R^{14}$, hydroxy, $-C(O)R^{15}$, aryl, heteroaryl, $-N^+(O^-)R^{13}R^{14}$, $-N(OH)R^{13}$, and $-NHC(O)R^a$ (wherein R^a is unsubstituted alkyl, haloalkyl, or aralkyl);

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^{13} and R^{14} may combine to form a heterocyclo group;

R^{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R^{16} is selected from the group consisting of hydroxy,

$-C(O)R^{15}$, $-NR^{13}R^{14}$ and $-C(O)NR^{13}R^{14}$;

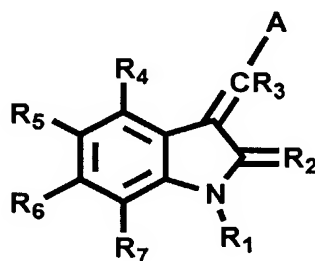
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R^{20} is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

[0122] A compound having the formula:



wherein:

R_1 is H;

R_2 is O or S;

R_3 is hydrogen;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$ or $CONRR'$;

n is 0-3;

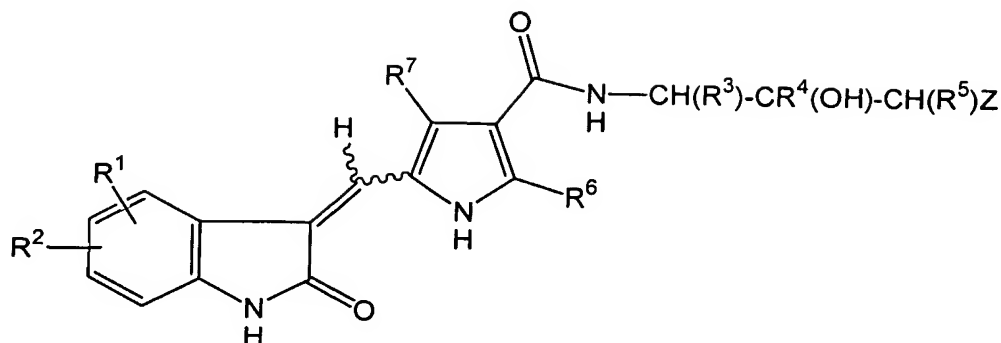
R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof.

[0123]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, $-C(O)R^8$, $-NR^9R^{10}$ and $-C(O)NR^{12}R^{13}$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)R^8$, $-S(O)_2NR^9R^{10}$ and $-SO_2R^{14}$ (wherein R^{14} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^3 , R^4 and R^5 are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently hydrogen or alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are attached from a heterocycloamino group;

R^6 is selected from the group consisting of hydrogen or alkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and $-C(O)R^{17}$ as defined below;

R^8 is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

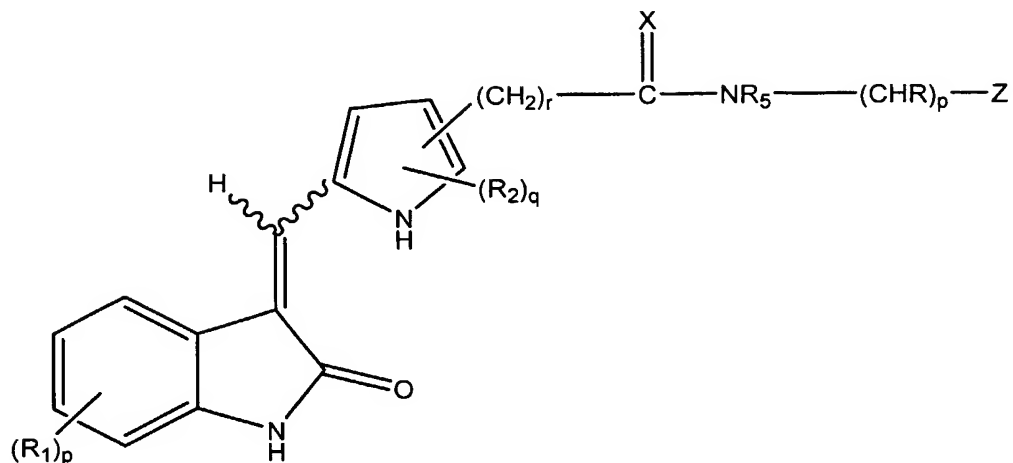
R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

[0124] In other embodiments of the invention, a mammal is exposed to a compound of Formula I:



(I),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$, $-NR_9R_{10}$, $-NR_9C(O)-R_{12}$ and $-C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, $-C(O)-R_8$, and SO_2R'' , where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$ and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

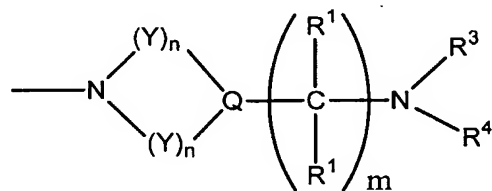
R_8 is selected from the group consisting of $-OH$, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of $-OH$, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

Q is C or N;

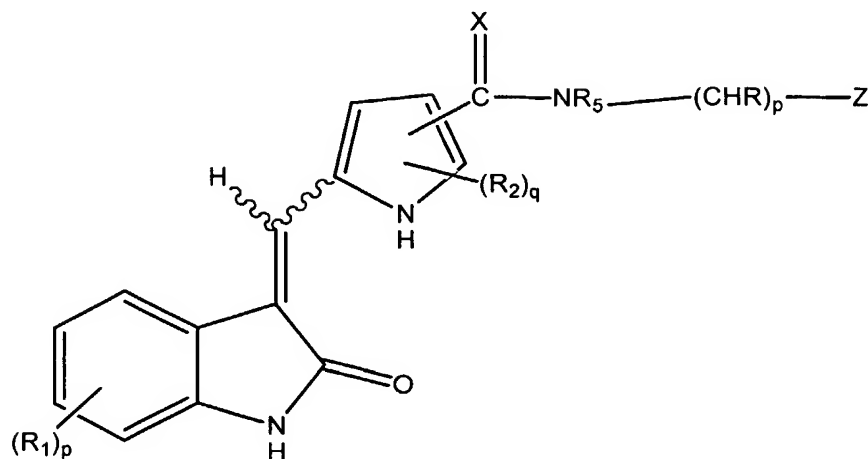
n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

[0125]

In another embodiment, a mammal is exposed to a compound of Formula II:



(II),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$, $-NR_9R_{10}$, $-NR_9C(O)-R_{12}$ and $-C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, $-C(O)-R_8$, and SO_2R'' , where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$ and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

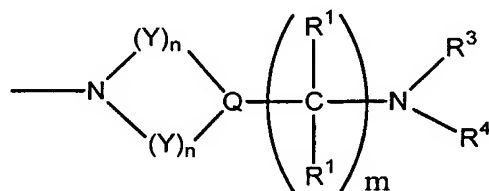
R_8 is selected from the group consisting of $-OH$, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of $-OH$, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH , O -alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

Q is C or N;

n is independently 0-4; and

m is 0-3;

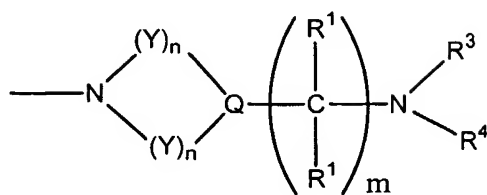
or a pharmaceutically acceptable salt thereof.

[0126] In another embodiment of the invention, a mammal is exposed to a compound of Formula I or II, wherein R_1 is halo (e.g., F and Cl) and Z is $-NR_3R_4$ wherein R_3 and R_4 are independently H or alkyl.

[0127] In another embodiment, Z of Formula I or II is $-NR_3R_4$, wherein R_3 and R_4 form a morpholine ring.

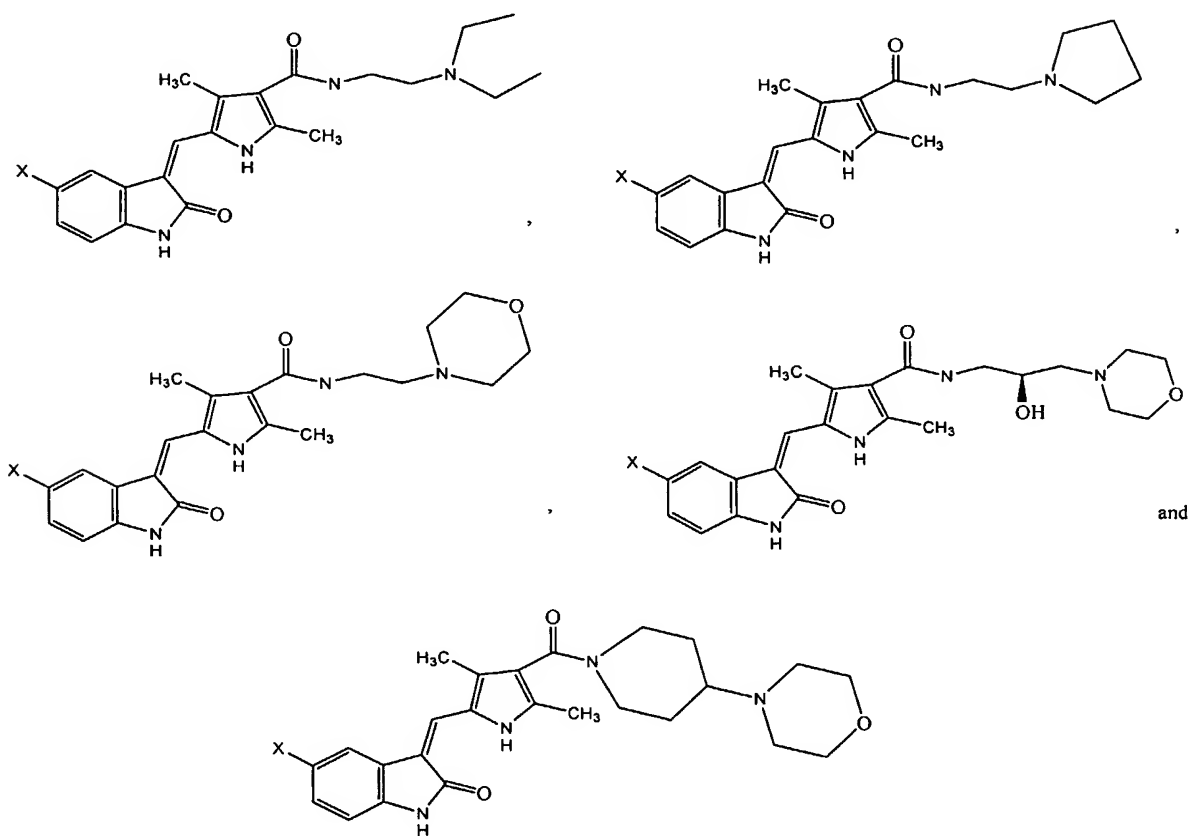
[0128]

In another embodiment, Z of Formula I or II is:



wherein each Y is CH₂, each n is 2, m is 0 and R₃ and R₄ form a morpholine ring.

[0129] In another embodiment of the invention, a mammal is exposed to a compound selected from the group consisting of



wherein X is F, Cl, I or Br; or a pharmaceutically acceptable salt thereof. In another embodiment, X is F.

[0130] In another embodiment of the invention, a mammal is exposed to a compound of Formula I selected from the group consisting of:

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound 2);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (Compound 3);

(S)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 4);

(R)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 5);

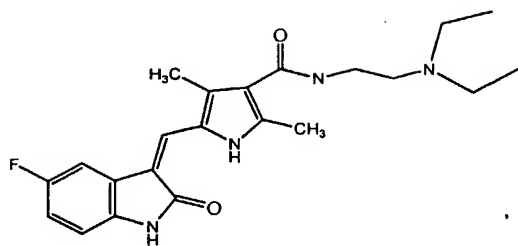
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 6);

5-(5-Chloro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 7);

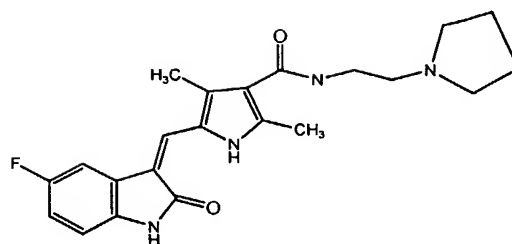
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethylamino-ethyl)-amide (Compound 8);

3-[3,5-dimethyl-4-(4-morpholin-4-yl-piperidine-1-carbonyl)-1H-pyrrol-2-methylene]-5-fluoro-1,3-dihydro-indol-2-one (Compound 9).

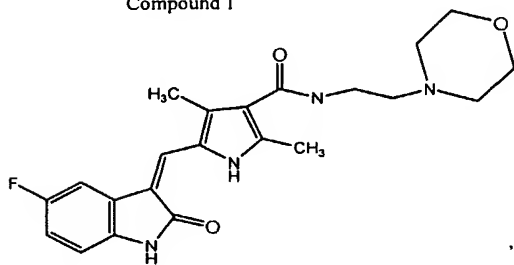
[0131] The above compounds are shown below:



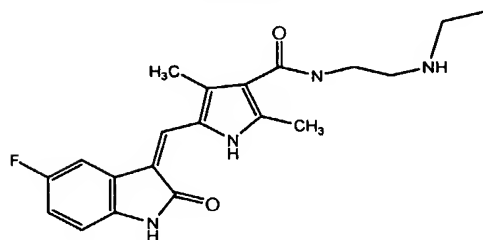
Compound 1



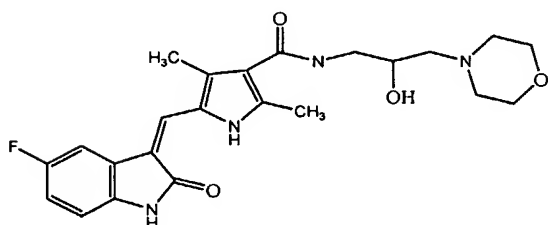
Compound 2



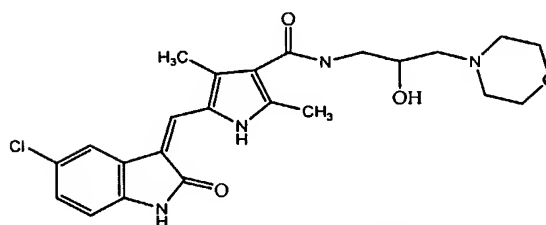
Compound 3



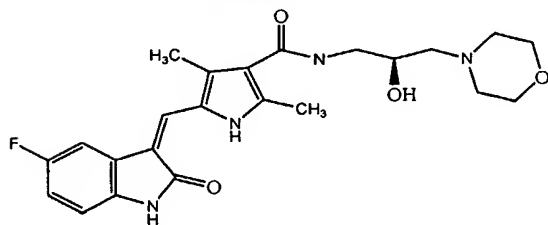
Compound 8



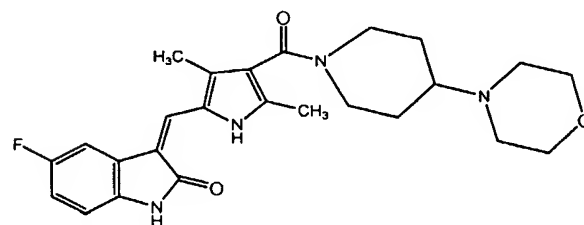
Compound 6



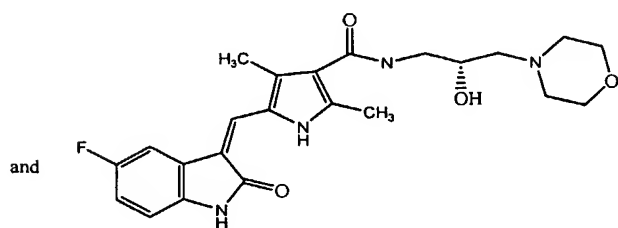
Compound 7



Compound 4



Compound 9



Compound 5

and

[0132] To clearly set forth the compounds of Formula I, Formula II and other compounds of the formulas described herein, useful in the inventive method, the following definitions are provided.

[0133] "Alkyl" refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 20 carbon atoms (whenever a numerical range; e.g. "1-20", is stated herein, it means that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). Alkyl groups containing from 1 to 4 carbon atoms are referred to as lower alkyl groups. When said lower alkyl groups lack substituents, they are referred to as unsubstituted lower alkyl groups. More preferably, an alkyl group is a medium size alkyl having 1 to 10 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, or tert-butyl, and the like. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more preferably one to three, even more preferably one or two substituent(s) independently selected from the group consisting of halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR,

RC(O)O-, and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, cycloalkyl, heterocyclic and aryl optionally substituted with one or more, groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups.

[0134] Preferably, the alkyl group is substituted with one or two substituents independently selected from the group consisting of hydroxy, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, or $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from the group consisting of hydrogen and alkyl. Even more preferably the alkyl group is substituted with one or two substituents which are independently of each other hydroxy, dimethylamino, ethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, morpholino, piperazino, 4-lower alkylpiperazino, phenyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolyl, triazinyl, and the like.

[0135] "Cycloalkyl" refers to a 3 to 8 member all-carbon monocyclic ring, an all-carbon 5-member/6-member or 6-member/6-member fused bicyclic ring or a multicyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with each other ring in the system) group wherein one or more of the rings may contain one or more double bonds but none of the rings has a completely conjugated pi-electron system.

[0136] Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, adamantane, cycloheptane, cycloheptatriene, and the like. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more

preferably one or two substituents, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen atoms of the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄ are as defined above.

[0137] "Alkenyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

[0138] "Alkynyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like.

[0139] "Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 1 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted.

When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, $RS(O)-$, $RS(O)_2-$, $-C(O)OR$, $RC(O)O-$, and $-NR_{13}R_{14}$, with R_{13} and R_{14} as defined above. Preferably, the aryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0140] "Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two, or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, $RS(O)-$, $RS(O)_2-$, $-C(O)OR$, $RC(O)O-$, and $-NR_{13}R_{14}$, with R_{13} and R_{14} as defined above. Preferably, the heteroaryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0141] "Heterocyclic" refers to a monocyclic or fused ring group having in the ring(s) of 5 to 9 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heterocyclic groups are pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, homopiperazino, and the like. The heterocyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted

lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄, with R₁₃ and R₁₄ as defined above. Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0142] Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0143] "Hydroxy" refers to an -OH group.

[0144] "Alkoxy" refers to both an -O-(unsubstituted alkyl) and an -O-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

[0145] "Aryloxy" refers to both an -O-aryl and an -O-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenoxy, pyridinyloxy, furanyloxy, thienyloxy, pyrimidinyloxy, pyrazinyloxy, and the like, and derivatives thereof.

[0146] "Mercapto" refers to an -SH group.

[0147] "Alkylthio" refers to both an -S-(unsubstituted alkyl) and an -S-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methylthio, ethylthio, propylthio, butylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, and the like.

[0148] "Arylthio" refers to both an -S-aryl and an -S-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenylthio, pyridinylthio, furanylthio, thientylthio, pyrimidinylthio, and the like and derivatives thereof.

[0149] "Acyl" refers to a -C(O)-R" group, where R" is selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted cycloalkyl, aryl optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihalomethyl, unsubstituted lower alkoxy, halo and -NR₁₃R₁₄ groups, heteroaryl (bonded through a ring carbon) optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and -NR₁₃R₁₄ groups and heterocyclic (bonded through a ring carbon)

optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and

$-NR_{13}R_{14}$ groups. Representative acyl groups include, but are not limited to, acetyl, trifluoroacetyl, benzoyl, and the like.

[0150] "Aldehyde" refers to an acyl group in which R" is hydrogen.

[0151] "Thioacyl" refers to a $-C(S)-R$ " group, with R" as defined herein.

[0152] "Ester" refers to a $-C(O)O-R$ " group with R" as defined herein except that R" cannot be hydrogen.

[0153] "Acetyl" group refers to a $-C(O)CH_3$ group.

[0154] "Halo" group refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

[0155] "Trihalomethyl" group refers to a $-CX_3$ group wherein X is a halo group as defined herein.

[0156] "Methylenedioxy" refers to a $-OCH_2O-$ group where the two oxygen atoms are bonded to adjacent carbon atoms.

[0157] "Ethylenedioxy" group refers to a $-OCH_2CH_2O-$ where the two oxygen atoms are bonded to adjacent carbon atoms.

[0158] "S-sulfonamido" refers to a $-S(O)_2NR_{13}R_{14}$ group, with R_{13} and R_{14} as defined herein.

[0159] "N-sulfonamido" refers to a $-NR_{13}S(O)_2R$ group, with R_{13} and R as defined herein.

[0160] "O-carbamyl" group refers to a $-OC(O)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0161] "N-carbamyl" refers to an $ROC(O)NR_{14}-$ group, with R and R_{14} as defined herein.

[0162] "O-thiocarbamyl" refers to a $-OC(S)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0163] "N-thiocarbamyl" refers to a $ROC(S)NR_{14}-$ group, with R and R_{14} as defined herein.

[0164] "Amino" refers to an $-NR_{13}R_{14}$ group, wherein R_{13} and R_{14} are both hydrogen.

[0165] "C-amido" refers to a $-C(O)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0166] "N-amido" refers to a $RC(O)NR_{14}$ group, with R and R_{14} as defined herein.

[0167] "Nitro" refers to a $-NO_2$ group.

[0168] "Haloalkyl" means an unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above that is substituted with one or more same or different halo atoms, e.g., $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like.

[0169] "Aralkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with an aryl group as defined above, e.g., $-CH_2phenyl$, $-(CH_2)_2phenyl$, $-(CH_2)_3phenyl$, $CH_3CH(CH_3)CH_2phenyl$, and the like and derivatives thereof.

[0170] "Heteroaralkyl" group means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with a heteroaryl group, e.g., $-CH_2pyridinyl$, $-(CH_2)_2pyrimidinyl$, $-(CH_2)_3imidazolyl$, and the like, and derivatives thereof.

[0171] "Monoalkylamino" means a radical $-NHR'$ where R' is an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., methylamino, (1-methylethyl)amino, cyclohexylamino, and the like.

[0172] "Dialkylamino" means a radical $-NR'R'$ where each R' is independently an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., dimethylamino, diethylamino, (1-methylethyl)-ethylamino, cyclohexylmethylamino, cyclopentylmethylamino, and the like.

[0173] "Cyanoalkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above, which is substituted with 1 or 2 cyano groups.

[0174] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycle group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

[0175] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0176] As used herein, a "physiologically/pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

[0177] An "pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0178] As used herein, the term "salt" of a compound of Formula I, II or other formulas or compounds described in this specification refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(i) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylaminoethyl)amide; or

(ii) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0179] "Method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

[0180] "In vivo" refers to procedures performed within a living organism such as, without limitation, a mouse, rat or rabbit.

[0181] "Treat", "treating" and "treatment" refer to a method of alleviating, ameliorating, abrogating or relieving a disease condition and/or any of its attendant symptoms.

[0182] "Patient" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

[0183] "Therapeutically effective amount" refers to that amount of the compound being administered which will prevent, alleviate, ameliorate or relieve to some extent, one or more of the signs or symptoms of the disorder being treated.

ADMINISTRATION AND PHARMACEUTICAL COMPOSITION

[0184] In another embodiment of the invention, a human patient is exposed or administered a compound of Formula I, Formula II or other formulas or compounds described in this application, or a pharmaceutically acceptable salt thereof. Alternatively, the compounds of Formula I, Formula II or other formulas or compounds described herein can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, PA., latest edition.

[0185] As used herein, "exposing," "administer" or "administration" refers to the delivery of a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof of this invention to a mammal.

[0186] Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. The preferred routes of administration are oral and parenteral.

[0187] Furthermore, one administer the compound in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor progenitor.

[0188] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0189] Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0190] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0191] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0192] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0193] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also.

[0194] Pharmaceutical compositions which may also be used include hard gelatin capsules. As a non-limiting example, compound 1 in a capsule oral drug product formulation may be as 50 and 200 mg dose strengths. The two dose strengths are made from the same granules by filling into different size hard gelatin capsules, size 3 for the 50 mg capsule and size 0 for the 200 mg capsule.

[0195] The capsules may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation must be stored at controlled room temperature (15-30°C).

[0196] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0197] The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0198] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection

suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0199] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

[0200] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[0201] In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

[0202] A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

[0203] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

[0204] Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0205] The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0206]

Examples of formulations for use in the present invention are in Tables A-C:

TABLE A

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide hard gelatin capsules				
Ingredient Name	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)	Amount in 75 mg Capsule (mg)	Amount in 200 mg Capsule (mg)
API	65.0	50.0	75.0	200.0
Mannitol	23.5	18.1	27.2	72.4
Croscarmellose Sodium^c	6.0	4.6	6.9	18.4
Povidone (K-25)	5.0	3.8	5.7	15.2
Magnesium Stearate	0.5	0.38	0.57	1.52
Capsule	-	Size 1	Size 3	Size 0

TABLE B

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules		
Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)
API	75.0	66.800^c
Mannitol	13.5	12.024
Croscarmellose Sodium^c	6.0	5.344
Povidone (K-25)	5.0	4.453
Magnesium Stearate	0.5	1.445
Capsule	-	Size 3

TABLE C

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules				
Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 25 mg Capsule (mg)	Amount in 50 mg Capsule (mg)	Amount in 100 mg Capsule (mg)
API^a	40.0	33.400^d	66.800^c	200.0^b
Mannitol	47.5	39.663	79.326	158.652
Croscarmellose Sodium^e	6.0	5.010	10.020	20.04
Povidone (K-25)	5.0	4.175	8.350	16.700
Magnesium Stearate	1.5	1.252	2.504	5.008
Capsule	-	Size 3	Size 1	Size 0

^a Drug substance quantity required for the batch will be adjusted to have 100% of labeled strength for capsules. Appropriate adjustment will be made to mannitol quantity to keep the same fill weight for each strength.

^b Quantity equivalent to 100 mg free base.

^c Quantity equivalent to 50 mg free base.

^d Quantity equivalent to 25 mg free base.

^e Half intragranular half extragranular.

which can be found in U.S. Patent Application Serial No. 10/237,966, filed September 10, 2002, now a provisional application, which is expressly incorporated in its entirety by reference.

[0207] Many of the compounds of Formula I, Formula II or other formulas or compounds described herein may be provided as physiologically acceptable salts wherein the compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium, salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide (Ca(OH)₂), etc.).

[0208] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, a therapeutically effective amount.

[0209] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0210] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of phosphorylation of CSF1R). Such information can then be used to more accurately determine useful doses in humans.

[0211] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the IC_{50} and the LD_{50} , wherein the LD_{50} is the concentration of test compound which achieves a half-maximal inhibition of lethality, for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0212] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from *in vitro* data, *e.g.*, the concentration necessary to achieve 50-90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[0213] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0214] At present, the therapeutically effective amounts of compounds of Formula I, Formula II or other formulas or compounds described in this application may range from approximately 25 mg/m² to 1500 mg/m² per day; alternatively about approximately 25 mg/m² to 1000 mg/m² per day. In another embodiment, the therapeutically effective amounts may range from approximately 25 mg/m² to 400 mg/m² per day.

[0215] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

[0216] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[0217] It is contemplated that the inventive method could be used in combination with other therapies, including chemotherapies, radiation therapies and surgical therapies for cancer. For combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the other agent can be determined by those of ordinary skill in the art, based on the effective amounts for the compounds described herein and those known or described for the other agent. The formulations and route of administration for such therapies and composition can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic and other agent in combination therewith.

[0218] Although all biomarkers disclosed in this specification are identified by specific sequences (and corresponding SEQ ID NOs), those skilled in the art will recognize that variants and alleles of these sequences also may function as biomarkers. Specific sequences, GenBank accession numbers and SEQ ID NOs in the specification are used to identify exemplary cDNAs, mRNAs and/or proteins of interest, and do not limit the invention to only those particular sequences. The biomarkers of the invention encompass variants and alleles of the disclosed sequences.

D. EXAMPLES – STUDIES USING COMPOUND A (SU6668)**1. Studies using Compound A – Materials and Methods****ELISAs**

[0219] Reagents for human tissue inhibitor of metalloproteinase 1 (TIMP-1), human active and pro-matrix metalloproteinase 9 (total MMP-9) and human vascular endothelial growth factor (VEGF) ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN). Human plasminogen activator inhibitor-1 (PAI-1) and human tissue factor (TF) ELISA kits were obtained from American Diagnostica, Inc. (Greenwich, CT). All ELISAs were performed on plasma samples according to the manufacturers' instructions.

2D gel analysis

[0220] Patient plasma was analyzed by 2D gel electrophoresis by Kendrick Labs (Madison, WI) according to the method of O'Farrell (J. Biol. Chem. 250: 4007-4021, 1975). Briefly, 150 ug of plasma protein was separated by isoelectric focusing using pH 4-8 gradient IEF gels. A 10% SDS/PAGE gel was used for the second gel dimension. Limited computerized comparisons were carried out on duplicate silver-stained gels and the spot percentage was calculated according to the formula: $\text{Difference} = (1 - \text{spot \% sample} \times \text{spot \% sample ref}) \times 100$. Spots whose abundance appeared to differ after Compound A exposure were subsequently excised and MALDI-TOF analysis was carried out for identification purposes.

Isolation of RNA from whole frozen blood

[0221] TRI Reagent®BD – RNA, DNA, protein isolation reagent was used according to the manufacturer's protocol, Molecular Research Center, Inc. (Cincinnati, OH) <www.mrcgene.com>.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0222] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/

expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total blood RNA (8 µg) of patient samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)₂₄ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for in vitro transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station. Images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0223] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1000 for these experiments). For comparisons between time points from a single patient, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the post-treatment sample was divided by the AD of the pre-dose samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 1.7 (increasing or decreasing).

TaqMan (qRT-PCR)

[0224] Primers and probes were designed using Primer Express 2.0 software, and purchased from Applied Biosystems (Foster City, CA). In all cases, primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). All probes contained a reporter dye (FAM) and a dye quencher (MGB). qRT-PCR was performed using 20 ng of total RNA with TaqMan® One-Step RT-

PCR Master Mix Reagents Kit (Applied Biosystems) following the manufacturer's protocol. The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. VEGF (Genbank accession number AF022375) transcripts were amplified using forward primer GCTCTCTTATTTGTACCGGTTTTTG (SEQ ID NO: 165), reverse primer AAGCTAGTGACTGTCACCGATCAG (SEQ ID NO: 166), and probe TCATGTTTCCAATCTC (SEQ ID NO: 167) to generate an 82-bp amplicon product. Vinculin (Genbank accession number M33308) transcripts were amplified using forward primer CCTGATATAAATGCAATATTAATGCCTTTA (SEQ ID NO: 168), reverse primer AAGAACCGGGAGAGCAAACAT (SEQ ID NO: 169), and probe ATCTATGCCAAAGATCACTT (SEQ ID NO: 170) to generate a 124-bp amplicon product. PECAM-1 (Genbank accession number L34657) transcripts were amplified using forward primer GGAGCACCGCCTGTGAA (SEQ ID NO: 171), reverse primer TGTGCGTTGCCTGAATGAAC (SEQ ID NO: 172), and probe ACCAACCTGAAGACAC (SEQ ID NO: 173) to generate a 56-bp amplicon product. MAPK Kinase 3 (Genbank accession number L36719) transcripts were amplified using forward primer TCTCGACTGAATGGACTTTGCA (SEQ ID NO: 174), reverse primer TTGTGTACCCCGCACCAA (SEQ ID NO: 175), and probe CACACCTCTATCCCGGC (SEQ ID NO: 176) to generate a 77-bp amplicon product. Hemoglobin, epsilon 1 (Genbank accession number AI349593) transcripts were amplified using forward primer GCTGCATGTGGATCCTGAGA (SEQ ID NO: 177), reverse primer TGAGTAGCCAGAATAATCACCATCA (SEQ ID NO: 178), and probe CTTCAAGCTCCTGGGTAA (SEQ ID NO: 179) to generate a 66-bp amplicon product. GAPDH and 18S were ordered as pre-developed assay reagents (PDARs) from Applied Biosystems and used as endogenous controls.

[0225] Data analysis of TaqMan (qRT-PCR): The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct scores for genes of interest for each sample were normalized against Ct scores for the corresponding endogenous control gene (GAPDH or 18S). Relative expression of specific transcripts in the post-dose sample compared to pre-dose sample was determined by the

following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta\text{Ct}},$$

Where $\Delta\Delta\text{Ct} = (\text{Ct}_{\text{target}} - \text{Ct}_{\text{control}})_{\text{post-dose}} - (\text{Ct}_{\text{target}} - \text{Ct}_{\text{control}})_{\text{pre-dose}}$.

2. Studies using Compound A – Results

ELISAs

[0226] Samples of plasma from human patients were taken before and 24 hours after the first dose of Compound A (SU6668). The patients were dosed twice over 24 hours with Compound A. The results of the ELISA analysis are shown in Figure 1, which shows that the levels of PAI-1, VEGF and TIMP-1 were increased in the plasma from patients exposed to Compound A. These proteins were therefore identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A. These patients were suffering from various types of cancer.

Two Dimensional Polyacrylamide Gel Electrophoresis

[0227] Samples of plasma from human patients suffering from advanced solid malignancies were taken before and 4 hours after the first (and only) dose of Compound A. A variety of proteins were increased and/or decreased in the plasma of patients treated with Compound A. As shown in Figures 2 and 3, mass spectrometry analysis identified one of these proteins (spot # 5) as ITIH4 (inter alpha (globulin) inhibitor H4). ITIH4 was therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A. See Figure 12 for sequences for ITIH4.

Microarrays and RT-PCR Analysis

[0228] Samples of whole blood from human patients suffering from advanced solid malignancies were taken before and 24 hours after the first dose of Compound A. An Affymetrix GeneChip analysis of the RNA transcripts present in patient blood before and after exposure to Compound A indicated that the levels of vinculin and VEGF RNA increase after exposure to Compound A (see Figure 4A and 4B). Vinculin and VEGF were therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A.

Microarrays and RT-PCR Analysis

[0229] Samples of whole blood from human patients were taken before and 27 days after the first dose of Compound A (in other words, samples were taken on day 0 and day 28; patients were dosed about 2 times per day on day 1-day 27, and following the first dose on day 28, the sample of blood was taken to measure biomarker(s). An Affymetrix GeneChip analysis of the RNA transcripts present in patient plasma before and after exposure to Compound A indicated that the levels of 26 transcripts were increased and/or decreased after exposure to Compound A (see Figure 5). Thus, 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A: eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792), Homo sapiens thymosin beta-10, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, human KIAA0195, Homo sapiens MAP kinase kinase 3 (MKK3), human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA). See Figure 12 for sequences for these biomarkers.

E. EXAMPLES – STUDIES USING COMPOUND B (SU5416)**1. Studies using Compound B – Materials and Methods****Study Population**

[0230] Patient samples were derived from 2 randomized, open-label, multicenter Phase III clinical trials comparing standard of care chemotherapy alone or combined with Compound B in patients with metastatic colorectal cancer. In both trials Compound B was delivered twice weekly at a dose of 145 mg/m² via I.V. infusion. In the first trial (designated Trial A), the standard of care chemotherapy consisted of weekly administration of 5-FU and leucovorin (Rosewell Park regimen); in the second trial (designated Trial B), the standard of care chemotherapy consisted of weekly or bi-weekly administration of 5-FU, leucovorin and

Irinotecan (CPT-11). A total of 23 patient sample pairs were included in Affymetrix microarray expression profiling analysis, 2 females and 9 males in the Compound B treatment arm, and 2 females and 10 males in the control arm. The median patient age was 66 and 65 years for the Compound B treatment arm and control arm, respectively. For RT-verification experiments, samples from 12 females and 24 males from the Compound B treatment arm, and 14 females and 17 males from the control arm were used. The median age for these patients was 62 and 60 years, respectively. Clinical response criteria were defined according to RECIST guidelines. Briefly, complete response (CR) is defined as complete disappearance of all measurable and evaluable clinical evidence of cancer; partial response (PR) is defined as at least a 50% reduction in the size of all measurable tumor areas; progressive disease (PD) is defined as an increase of $\geq 25\%$ (compared to baseline or best response) in the size of all measurable tumor areas; and stable disease (SD) is defined as neither sufficient shrinkage to quantify for PR nor sufficient increase to qualify for PD.

Patient samples

[0231] All clinical samples for biomarker analysis were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the study informed consent prior to any study related procedures. All blood samples were collected into Vacutainer tubes containing sodium heparin. Ten 10 ml of blood was withdrawn from patients prior to receiving any treatment on day 1 and also prior to dosing at end of cycle 1 (day 56 in Trial A; day 42 in Trial B). For peripheral blood mononuclear cell (PBMC) preparations, blood samples were shipped overnight at ambient temperature to a central processing facility (Quest Diagnostics, Inc., Collegeville, PA, USA) for PBMC isolation via Ficoll gradient method. Purified PBMCs were shipped in RNA lysis buffer (Clontech, Palo Alto, CA, USA) to SUGEN where isolation of total RNA was performed. For Trial B, whole peripheral blood samples were directly frozen at the clinical sites and shipped on dry ice to SUGEN for RNA isolation.

RNA sample processing

[0232] Total RNA was purified from PBMC samples using Clontech Nucleospin RNA II kit reagents (Clontech, Palo Alto, CA) and from whole blood samples using MRC

TRI Reagent BD (Molecular Research Center, Cincinnati, OH, USA), an adaptation of the Chomczynski single step method, according to the manufacturer's instructions. All sample preparations included a treatment with RNase-free DNase. RNA yields were measured by UV absorbance and RNA quality was assessed by agarose gel electrophoresis with ethidium bromide staining for visualization of ribosomal RNA band integrity.

Affymetrix high-density oligonucleotide microarray analysis of PBMC expression profiles

[0233] In general, the standard RNA processing and hybridization protocols as recommended by Affymetrix (Santa Clara, CA, USA) were followed in this study; these protocols are available in the Genechip® Expression Analysis Technical Manual (viewable at <www.affymetrix.com/support/technical/manual/expression_manual.affx>. Yields of total RNA for PBMC samples were generally low and for the majority of patients it was not possible to use the standard amount of total RNA ($\geq 5 \mu\text{g}$) as recommended in the standard protocol. Therefore a double linear amplification approach was used in the generation of cRNA for hybridization. In these experiments, equal amounts of starting material were used for pre- and post-treatment samples from each donor (typically $2 \mu\text{g}$). Briefly, the protocol was as follows: double-stranded cDNA was synthesized from total RNA ($2 \mu\text{g}$), with Invitrogen Life Technologies SuperScript Choice system reagents (Invitrogen, Carlsbad, CA). The T7-(dT)₂₄ oligomer was used for priming first-strand cDNA synthesis. Double-stranded cDNA product was purified via phenol-chloroform extraction, then used as template in first round of in vitro transcription (IVT) of cRNA. The IVT reaction was performed with BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol but with substitution of non-biotinylated ribonucleotides for biotinylated ribonucleotides. The cRNA product was then purified with Qiagen spin column clean-up protocol and used as template in second round of cDNA synthesis. This second round of synthesis was similar to the first round except that random hexamers were used in priming of first-strand synthesis, with T7-(dT)₂₄ oligomer priming the second-strand. Purification of the cDNA was as in the first round. The second round of IVT of cRNA was as in the first round but with biotinylated ribonucleotides rather than non-biotinylated ribonucleotides. Purified cRNA was quantitated, chemically fragmented according to Affymetrix protocol, and then hybridized overnight on Human Genome U95A Arrays (which contain probe sets for the detection of approximately 12,600

transcripts). Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station, then images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0234] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The key output from individual arrays are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays. Average Difference determination relies on difference between background-subtracted signal from perfect match (PM) oligos and corresponding mismatch control (MM) oligos within a probe set representing a given transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a Scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (which was set at 1500 for these experiments). For comparisons between time points from a single patient, batch files were generated with Microarray Suite. These files contain calculated fold change (FC) values, which represent differential expression ratios of day 56 compared to baseline, and also Difference Calls (DC), which represent a more conservative estimate of differential expression, with qualitative scores assigned to each transcript measurement according to the following system: Increased (I), Marginally Increased (MI), No Change (NC), Marginally Decreased (MD), and Decreased (D).

[0235] Subsequent data analysis was performed primarily with Spotfire DecisionSite for Functional Genomics software (version 7) package and its Array Explorer component (Spotfire, Somerville, MA). Hierarchical clustering analysis and statistical comparisons were included in this step. Further refinement of the data, including filtering by Difference Call scores, was done with the Microsoft Access 97 database analysis program.

SYBR Green quantitative RT-PCR verification of array results

[0236] Primers were designed with Primer Express 1.5 software (Applied Biosystems). In all cases, primers were designed to bind within the sequence that was used in Affymetrix probe set designs (target sequence information available on Affymetrix NetAffx website). Total RNA samples (1 µg) were reverse transcribed to yield first-strand cDNA using the Applied Biosystems Reverse Transcription Reagents protocol (Applied Biosystems, Foster City, CA). The reverse transcription reactions were then diluted 1:5 in distilled H₂O.

SYBR Green PCR reactions were performed in 96-well optical plates and run in an ABI PRISM® 7700 Sequence Detection System (SDS) machine. For individual reactions, 10 µl of each sample were combined with 15 µl of SYBR Green PCR Master Mix (Applied Biosystems) containing the appropriate primer pair at 350 nM. Data was extracted and amplification plots generated with ABI SDS software. All amplifications were done in duplicate and threshold cycle (C_t) scores were averaged for subsequent calculations of relative expression values. The C_t scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. Heat dissociation curve analysis was performed after each SYBR Green run as a test of whether a single product had been generated in each PCR reaction; multiple peaks in the dissociation curves are indicative of multiple PCR products and thus reduced specificity and sensitivity.

Quantitation and statistical analysis of SYBR Green PCR data

[0237] The C_t scores for genes of interest for each sample were normalized against C_t scores for the corresponding endogenous control gene, which was the β -glucuronidase (GUS) gene in these experiments. Relative expression for day 56 compared to day 1 was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta C_t},$$

Where $\Delta\Delta C_t = (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 56}} - (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 1}}$.

[0238] The relative expression data for a select subset of potential biomarkers were tested for differences between the Compound B (treatment) and the standard of care (control) arms. The Mann-Whitney U Test with a critical alpha level of 0.05 was used for statistical significance. Individual genes observed to be significantly different by Affymetrix analysis and in both sets of SYBR Green RT-PCR experiments were screened as potential biomarker candidates. This subset of potential biomarker candidates was tested subsequently for utility as class predictors to discriminate between the Compound B and standard of care arms. Discriminant analysis, a multivariate statistical technique, was used for this purpose. The genes were tested individually, using all possible combinations, by reducing dimensions (Principal Component Analysis) in order to determine the subset of genes (predictor variables) that yielded highest classification accuracy. Cross-validation was used to test the robustness of classification accuracy. Results from three different cross-validations were evaluated to select the best set of predictable biomarkers: (1) jackknife method (dropping

one case at a time); (2) randomly splitting the pooled data into two halves, prediction (for building model) and validation (for testing model); and (3) using the first trial as prediction and the later trial as validation sets, respectively. All statistical analyses were carried out after natural-log transformation on the data; SYSTAT 9.01 (SPSS, Inc., Chicago, IL, USA) software was used in statistical analysis.

2. Studies using Compound B – Results

Affymetrix expression profiling of pre- and post-treatment matched PBMC samples

[0239] Expression profiling using Affymetrix high-density oligonucleotide microarrays was applied to PBMC samples harvested from patients in a Phase III clinical trial of Compound B in Trial A. The PBMC samples were harvested at baseline (day 1) and at end of cycle 1 (day 56) from patients receiving standard-of-care (5-FU/leucovorin) treatment and from those receiving standard-of-care plus Compound B. Sample pairs from 23 patients were processed and the dataset was filtered for expression changes that consistently correlated with the treatment arm (Compound B). Of 13 genes that met the initial requirement, 6 were further tested by quantitative RT-PCR analysis of additional patient samples from patients.

[0240] Table 1 includes a summary of the total samples processed. As RNA yields rarely exceeded 2 µg, a double amplification step was used in cRNA generation for the samples that were used (see Materials and Methods). Only samples from patients with cycle 1 responses of either PR/CR or PD were used in the final dataset.

[0241] Batch comparison files were generated for each day 1/day 56 sample pair after hybridization. Batch comparisons included both fold change (FC) values as calculated by Affymetrix Microarray Suite software as well as difference calls (DC). DC offer a more stringent but non-numerical measure of whether levels of a transcript are different in the 2 samples. Batch comparison results for the 23 cases were analyzed with Spotfire Decision Site software tools. Initial analysis suggested there was more similarity among patient samples of the same treatment arm than among samples of the same response category (PR/CR or PD) independent of treatment arm. Therefore, subsequent analysis focused on identification of transcripts that were differentially expressed in the Compound B arm but not in the control arm.

[0242] The Treatment Comparison tool in Spotfire was used to identify transcripts that were statistically significantly different in the two treatment arms; this tool uses t-test analysis of averaged fold changes for each group. To further refine this subset of genes, queries based on DC status were performed with Microsoft Access. The data were filtered to identify those genes that were called 'Increased' (I) or 'Decreased' (D) in a majority of the Compound B arm cases. A group of 13 genes that frequently showed increased expression was identified. Figure 6 displays a schema of the DC scores assigned to each gene for each patient sample pair. All cases from the Compound B arm show induction in at least 6 of the 13 genes.

[0243] Table 2 includes a brief summary of putative biological function for each of the 13 gene products, as well as an ID number assigned by Affymetrix to each transcript-specific probe. The last two columns in Table 2 list the number of patients in which transcript levels were increased at day 56 relative to day 1 (i.e., an 'Increase' call was assigned). Total number of patients is 11 for the Compound B (SU5416) arm and 12 for the control arm. The average fold change of all of these transcripts was higher in the Compound B (SU5416) arm (the lowest average fold change was 2.6 for hypothetical protein FLJ13052, the highest was 33 for lactoferrin); the range of fold changes was also broader in this category, presumably representing variability among patients.

Quantitative RT-PCR validation of differentially expressed transcripts

[0244] To validate the microarray results, a subset of these transcripts was chosen for quantitative RT-PCR analysis. Primer sets were designed for 6 of the 13 genes; matrix metalloproteinase-9 (MMP-9), thrombospondin-1 (TSP-1), CD24, defensin α 3, lipocalin 2 (LCN2), and lactoferrin. These 6 genes were chosen based on potential roles of encoded proteins (for example, thrombospondin-1 and MMP-9 have known roles in angiogenesis) or because of the degree to which they appeared to be differentially regulated between treatment arms. The lipocalin-2 gene (LCN2) has been reported to be inducible by dexamethasone (Science, 293: 829-34 (2001)). Dexamethasone is one of the premedications administered to patients in the Compound B arm. Table 3 describes the forward and reverse primers that were used in validation of these transcripts.

[0245] SYBR Green chemistry was used to validate the microarray expression profiling data. SYBR Green is a dye that fluoresces when bound to double-stranded DNA,

thus signal is directly proportional to the amount of product formed during PCR amplification. This method allows rapid and inexpensive comparison of gene expression across a large number of samples. The qRT-PCR validation was performed with a total of 31 Compound B patient sample pairs, 8 of which had previously been analyzed on Affymetrix U95A arrays and thus allowed a comparison of the correlation between the 2 transcript profiling methods. Of the 31 samples, 18 were from the Compound B arm and 13 were from the control arm.

[0246] Data for each gene was normalized to expression of a housekeeping gene, β -glucuronidase (GUS). By direct comparison of SYBR Green RT-PCR results and Affymetrix results from the same cases, the overall qualitative correlation (i.e., same trend of induction or no change detected in both samples) was greater than 70%. This number is perhaps an underestimate since results for one patient were completely discordant between methods and thus potentially due to experimental artifact.

[0247] Figure 7 summarizes the results from the RT-PCR validation and compares them with those from the Affymetrix analysis. It is clear that there are some differences in the trends displayed in the 2 datasets. This is further demonstrated by statistical analysis, as Mann-Whitney U test comparison of Compound B and control results from both analyses indicates that only 4 of the 6 genes display statistical significance (Table 4). These 4 genes are CD24, lactoferrin, LCN2, and MMP-9. (MMP-9 exhibited a p-value that was close to the significance cutoff and thus was also selected for further analysis.)

Qualitative RT-PCR validation of differentially expressed transcripts with samples from a second Phase III Compound B trial

[0248] To further confirm these transcripts as biomarkers of Compound B administration, SYBR Green RT-PCR analysis of these 4 transcripts was carried out in a collection of samples from a second Phase III trial (Trial B). In this randomized metastatic colorectal cancer study, 5-FU/leucovorin/CPT-11 was administered as the standard of care, and compared to the standard of care plus Compound B. RNA samples from patients in this trial were derived from frozen whole blood (rather than purified PBMCs), and harvested at the beginning (pre-dose day 1) and at the end (day 42) of cycle 1. To test if similar results occurred, analysis was performed on 36 sample pairs, 18 from Compound B arm and 18 from control arm. Due to limited numbers of available samples, many of the cases analyzed in this

analysis were from patients with stable disease (SD) at cycle 1 assessment rather than PR/CR and PD as in the previous approaches.

[0249] Figure 8 summarizes the overall behavior of the transcript levels in both trial arms in terms of the frequency with which the transcripts showed an induction (here defined as relative expression, day 42 vs day 1) of 2-fold or greater in each arm. It is clear that there is more induction of these transcripts at day 42 in the Compound B arm than in the control arm. This is also reflected in statistical analysis, as indicated in results of the Mann-Whitney U Test of this dataset (Table 5).

[0250] A visual representation of hierarchical clustering analysis of the qRT-PCR relative expression values from both trials for each of the transcripts is displayed in Figure 9. This clustering pattern displays the distinction between the Compound B and control arms based on relative expression data, and also indicates further distinctions among subsets of patients as well as the degree of overlap between trial arms in the clustering pattern. The extent of similarity between the relative expression patterns for each transcript (represented in columns) is also indicated; the pattern of MMP-9 is distinct from the others as it appears in a separate branch in the dendrogram structure.

Discriminant analysis of the classification power of biomarkers

[0251] We tested whether relative expression data from these samples could be used in a predictive fashion to classify samples to the appropriate trial arm. To test this, discriminant analysis of the SYBR Green RT-PCR data was performed. Relative expression values from both the first and the second dataset were combined, after comparison of mean relative expression ratios and standard deviations indicated greater similarity between respective trial arms rather than between control and Compound B arm in either trial alone. The relative expression ratios were then natural log-transformed to reduce the scale of the values and thus make control and treated arms more comparable. When the samples were pooled (67 cases altogether) and subjected to classification prediction, a total prediction accuracy of 84% was achieved. Further cross-validation was performed by the jack-knife method (which does a series of predictions, randomly removing 1 case from the total each time), and by splitting the data set into 2 random halves (one a 'training' set and the other a 'testing' set).

[0252] The results from each of these steps are summarized in Table 6 for a set of 3 of the 4 transcripts that gave the best accuracy percentage (including MMP-9 slightly reduced the accuracy of cross-validation). Thus, it is predicted that expression data from these 3 genes would accurately distinguish Compound B arm patients from control arm in between 67% to 84% of cases. When the first trial data was used as the 'training' set and the second trial data as the 'testing', as opposed to randomly selecting the data, the % accuracy in cross-validation was 86% and 77% for the training and testing set, respectively. Cross-validation results are displayed for two different approaches. In section 2 of Table 6, one case is dropped at a time and its group membership predicted from the other cases. In sections 3 and 4, cross-validation is carried out by using a randomly selected half of the cases as a training set and the remaining half as a test set. Section 4 summarizes the prediction accuracy achieved when the group in section 3 is used as a training set.

Conclusions: Compound B Studies

[0253] Large-scale gene expression analysis was applied to blood RNA samples from a clinical trial of Compound B to investigate changes in gene expression that might correlate with exposure to cancer therapy. Independent quantitative RT-PCR validation of initial array hybridization results was performed on larger sample populations from two conceptually similar Phase III clinical trials using Compound B. A set of 4 transcripts (CD24, lactoferrin, LCN2, and MMP-9) was identified whose expression was significantly induced at the end of one treatment cycle relative to baseline following Compound B administration. Discriminant analysis indicates that data derived from the RT-PCR study would have a class prediction accuracy of at least 70%.

[0254] These 4 transcripts are considered to be biomarkers of Compound B administration and other compounds that inhibit tyrosine kinase. These results also demonstrate that human blood samples can serve as surrogate tissues for biomarker investigations and that large-scale gene expression analysis is a useful approach for characterization of clinical trial samples.

F. EXAMPLES – FURTHER STUDIES USING COMPOUND B (SU5416)**Baseline and post-treatment levels of PAI-1 in Compound B patient plasma**

[0255] PAI-1 plasma levels were examined in samples from Compound B patients. Interestingly, median PAI-1 levels decreased after 56 days of treatment in samples from all patients examined with a MR (minor response) at the end of cycle 1 (Figure 10, n = 37; Compound B arm day 1 median 40.66 ng/ml, day 56 median 23.93 ng/ml, 5FU/LV arm day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml). In contrast, median PAI-1 levels in samples from all patients examined with a PD (progressive disease) response at the end of cycle 1 did not appear to change significantly (Figure 10, n = 47; Compound B arm day 1 median 26.47 ng/ml, day 56 median 34.8 ng/ml, 5FU/LV arm day 1 median 25.67 ng/ml, day 56 median 23.29 ng/ml). Furthermore, the decrease in PAI-1 plasma levels in the control arm MR patients after 56 days of treatment was statistically significant (day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml, $P = 0.0003$; n = 20). The decrease in PAI-1 levels of Compound B arm patients was not statistically significant ($P = 0.095$; n = 17). These data indicate that changes in plasma PAI-1 levels after one cycle of treatment correlate with cycle one clinical response of both the experimental and control arm regimens.

Pre-treatment levels of PAI-1

[0256] An analysis of the pre-treatment plasma levels of plasminogen activator inhibitor-1 (PAI-1) shows that pre-treatment levels also correlate with clinical response (on day 56) in either arm, indicating that PAI-1 is a biomarker predictive of response to tyrosine kinase inhibitor in advanced colorectal cancer.

[0257] An analysis of the pre-treatment levels of PAI-1 indicated that patients with an MR response (cycle 1) had a statistically significantly ($P = 0.001$) higher level of plasma PAI-1 (median 41 ng/ml; n = 37) than that of patients with a PD response (median 26 ng/ml; n = 47) regardless of the regimen subsequently received. Thus far, only 4 patients that had a partial response (PR) at the end of cycle 1 have been examined for PAI-1 plasma levels. These patients have pre-treatment levels (median 37.4 ng/ml) similar to the MR patients (median 40 ng/ml), however PAI-1 levels did not decrease significantly in these patients samples after 56 days of treatment. These results (see Figure 10) indicate that the pre-treatment levels of plasma PAI-1 are predictive of MR response (as compared to a PD response) to either the experimental or the control arm regimen.

[0258] The present invention includes a method for predicting the probability of whether a patient will respond positively to administration of a tyrosine kinase inhibitor, comprising measuring the level of PAI-1 in patient plasma, wherein a level of greater than 30 nanograms/per ml of plasma, or greater than at least 35 nanograms, or greater than at least 37 nanograms per ml, indicates a positive probability that the patient will respond positively to administration of a tyrosine kinase inhibitor.

G. EXAMPLES – STUDIES USING COMPOUND 1

1. Studies using Compound 1 – Materials and Methods

[0259] A panel of proteins were investigated for their utility as biomarkers of Compound 1 in cancer patients receiving the compound in Phase I trials. The patient samples were from a total of four Phase I trials, 3 of which were open to patients with any advanced solid malignancy (these were Trials A, B and C) and one of which (Trial D) was a trial in patients with Gleevec-refractory, resistant, or intolerant gastrointestinal stromal tumors (GIST). In all cases, plasma samples were available from just before first Compound 1, or malate salt thereof, dose (baseline) and at various time points during dosing. In Trials A and B, patients received Compound 1. In Trials C and D, patients received a malate salt of Compound 1. For methods of making Compound 1, *see* U.S. Ser. No. 09/783,264 or WO 01/60814, U.S. Ser. No. 10/076,140 or U.S. Ser. No. 10/281,985, the disclosures of which are incorporated by reference. For methods of formulating Compound 1, *see* U.S. Ser. No. 10/237,966 (now a U.S. provisional application), the disclosure of which is incorporated by reference.

[0260] All of the ELISA-based screening of candidate proteins were performed with commercially available ELISA kits; the kits for the biomarkers described in this report are all available from R&D Systems (Minneapolis, MN). A commercially available membrane array containing antibodies for the detection of 42 human cytokines was also used in screening of a patient's plasma samples before and after treatment. The antibody array used in cytokine screening (RayBio Human Cytokine Array III) was from RayBiotech (Norcross, GA).

[0261] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol. Study participants signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood

samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site. The time points for which plasma samples are available in each trial are as follows:

Trial A (4 weeks on/ 2 weeks off dosing schedule):
plasma – Day 1 (0, 6, 24 hr); Day 28 (0, 6, 24 hr)

Trial B (2 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6, 12, 24 hr); Day 13 (0, 6, 12, 24 hr)

Trial C (4 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6 hr); Day 15, 29, 42* (Cycle 1); Day 1, 15, 29 (Cycle 2)

Trial D (2 weeks on/ 2 weeks off):
Plasma – Day 1, 7, 14, 28* (Cycle 1); Day 1 only, in subsequent cycles

Trial E (4 weeks on/2 weeks off):
Plasma – Day 1, 3, 28 (Cycle 1)

* ‘washout’ sample

Plasma samples were also collected from a set of 10 SUGEN healthy donors; plasma was collected at 3 time points for each donor (day 1, 14, and 28) to mimic time points used in the Phase I trials and thus serve as controls for the normal level of fluctuation of plasma markers in the absence of Compound 1 treatment.

[0262] Data analysis was performed for each marker. This was done by generating ratios of plasma levels at various time points during treatment versus the plasma levels at baseline (pre-dose on day 1, cycle 1), or by comparing absolute plasma concentrations at times during treatment to the baseline absolute plasma concentrations. For correlative analysis, scatter plots were drawn and linear regressions were calculated comparing fold change (end of cycle 1 dosing to baseline) of each marker to corresponding values assigned to clinical parameters such as pharmacokinetics, drug dosage, and ¹⁸FDG-PET functional imaging.

2. Studies using Compound 1 – Results

[0263] A panel of candidate proteins was evaluated by ELISA analysis in plasma samples from cancer patients receiving Compound 1 or malate salt thereof. Of those investigated, a subset was observed to change consistently in patients receiving Compound 1 or malate salt thereof. One of the proteins was Vascular Endothelial Growth Factor (VEGF);

large increases (greater than 3-fold) in plasma levels were seen in approximately 70% of patients in Trials A, B and C, and in a small proportion of patients in Trial D.

[0264] Figure 13 displays typical pattern of VEGF plasma levels seen in Trial C. VEGF levels are observed to rise by day 15 of cycle 1 and typically peak at day 29, then tend to subside to near baseline levels by day 42, which is the end of the 2-week drug rest period, or 'washout', in these patients.

[0265] To further investigate this, levels of a related angiogenic factor, Placenta Growth Factor (PLGF), were measured in some of the same patients as in the VEGF tests. As shown in Table 7, levels of PLGF are induced in a majority of patient samples that were tested, and follow a similar pattern as VEGF in that levels are most induced at day 29 and decline by day 42.

[0266] A further question regarding VEGF and PLGF was whether the presence of VEGF/PLGF heterodimers in patients' plasma could be detected, and whether levels of the heterodimer could be modulated by treatment with Compound 1 or malate salt thereof. Heterodimers of VEGF and PLGF have been reported in the scientific literature. To measure heterodimers, a hybrid ELISA assay was used, combining reagents from both the R&D Systems VEGF and PLGF ELISA kits (where VEGF antibodies are used in capture step and PLGF antibodies are used in detection step).

[0267] The results of applying this assay to plasma samples from 3 patients are shown in Figure 14. Data from the same samples for VEGF and PLGF are also shown in the graphs in Figure 14. A similar pattern of induction of the VEGF/PLGF heterodimer as was seen for VEGF and PLGF was observed. In 3 of 3 patients tested, an increase in plasma levels of VEGF/PLGF heterodimer is observed, indicating that both PLGF and the VEGF/PLGF heterodimer are novel biomarkers of Compound 1 activity in patients.

[0268] Another protein, VEGF receptor 2 (VEGFR2) was investigated. VEGFR2 is one of the targets of Compound 1 and is important in angiogenesis. Whether soluble VEGFR2 is detectable via ELISA in plasma samples from cancer patients was investigated, as well as whether levels of the protein would change in response to treatment with Compound 1 or malate salt thereof.

[0269] Intriguingly, levels of the plasma soluble form of VEGFR2 were observed to decrease in the vast majority of patients (greater than 90%) in Trials A, B and C at chronic time points (13 days or more) after the start of treatment with Compound 1 or malate salt

thereof. Also, in Trial D, a dose-dependency of the sVEGFR2 decrease was seen, as changes were clearly observed in a cohort of patients in that trial receiving 50 mg daily doses of a malate salt of Compound 1, but not observed in a cohort of patients receiving 25 mg daily doses (Figure 15). The difference between the dose cohorts was statistically significant as judged by t-test. Also, levels of sVEGFR2 typically increased to near baseline levels at the end of the 2-week drug rest period in patients from all 4 trials, thus exhibiting a pattern similar in timing but opposite in direction to that seen for VEGF and PLGF (Table 9). Table 9 displays results for sVEGFR2 in individual patients, and also includes results for PLGF where available. Also included in Table 9 is information on the types of cancers found in the patients.

[0270] Further, data suggests that there exists some correlation between the extent of decrease in plasma sVEGFR2 and pharmacokinetics measurements of drug exposure in patients. This is demonstrated in Figure 16, which shows a scatter graph plotting change in sVEGFR2 plasma level (ratio of level on last day of cycle 1 dosing to baseline level) against area under curve (AUC) drug exposure measurements (from last day of cycle 1 dosing). The graph is a composite of data from all 4 trials, and the R-squared value indicates there is some association between decrease in sVEGFR2 and drug exposure. Thus, soluble VEGFR2 is a novel marker of Compound 1 treatment and may be a marker of both drug exposure and biological activity of the compound.

[0271] Another potential biomarker of Compound 1 was identified first in an array-based screen of plasma samples, before and after Compound 1 treatment, from a patient in Trial B. The array screen utilized a commercially available antibody membrane array, which in principle allows for simultaneous measurement of 42 different human cytokines. Results of the screen indicated that levels of a protein called Monokine Induced by Interferon-gamma, or MIG, were significantly higher after treatment with Compound 1 than in baseline samples. This result was confirmed via an MIG ELISA assay on the same patient samples. Following confirmation, levels of MIG in plasma were assessed for a number of patients from Trial C. These results showed that MIG was induced more than 3-fold in 30-40% of the patients tested (data not shown).

[0272] There is evidence of a correlation between increased MIG levels and a positive response in the functional imaging assay of ¹⁸FDG-PET (a feature of Trials C and D). This is illustrated in Figure 17; those patients with at least a mixed response based on PET imaging tended to have higher folds of induction of secreted MIG protein. To further

investigate the induction of MIG observed in patients, we have also measured the plasma levels of IP-10 and I-TAC before and after treatment with Compound 1 or malate salt thereof. IP-10 and I-TAC, like MIG, are regulated at the expression level by interferon-gamma, and both IP-10 and MIG have roles in chemoattraction of immune cells and exhibit angiostatic (anti-angiogenic) activity. Interestingly, evidence suggests that MIG and IP-10 are induced in tandem in 6 of 6 patients checked for both proteins while MIG and I-TAC are induced in tandem in 5 of 5 (Table 8). Similarly, all 3 proteins are induced in the 2 patients where all of the 3 were checked (Table 8). Table 10 indicates the types of cancer found in patients where MIG is induced. Thus, evidence indicates that MIG, IP-10 and I-TAC are novel biomarkers that are modulated in Compound 1 patients and are markers that correlate with an anti-tumor response as measured by PET imaging.

[0273] In summary, ELISA-based screening of plasma samples from Phase I clinical trials using Compound 1, or malate salt thereof, has yielded a set of circulating proteins that are novel surrogate markers for Compound 1 drug exposure and/or biological activity. Soluble VEGFR2 has been identified in plasma as a marker of drug exposure, while VEGF, PLGF, and VEGF/PLGF heterodimers have been frequently observed to increase in a majority of patients and appear to be correlates of biological activity and (to a lesser extent than sVEGFR2) drug exposure. MIG, IP-10 and I-TAC are additional biomarkers that appear to correlate with anti-tumor activity as measured by ¹⁸FDG-PET functional imaging.

H. EXAMPLES – FURTHER STUDIES USING COMPOUND 1

1. Further studies using Compound 1 – Materials and Methods

In Vivo Animal Studies

[0274] Female athymic-*nu/nu* mice (Charles River, Hollister, CA) were injected with Colo205 human colon cells (5×10^6 cells) subcutaneously. The animals were treated with a single dose of either citrate vehicle or Compound 1 at 40 mg/kg when the tumors are approximately 350-400 mm³ in size. For biomarker studies, tumors were harvested at six and 24 hours post-treatment and snap frozen for RNA extraction.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0275] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, total RNA from tumor samples was prepared using Nucleospin RNA II Kit in accordance with the manufacturer's recommendation (Clontech, Palo Alto, CA). RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total RNA (8 µg) of tumor samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)₂₄ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for *in vitro* transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station.

Images were scanned with a Hewlett-Packard GeneArray scanner. All techniques were performed on xenograft tissue samples according to the manufacturers' instructions.

Data analysis of DNA microarray

[0276] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1500 for these experiments). For comparisons between different treatments from a single time point, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the drug-treated samples was divided by the AD of the vehicle-treated samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 2.0 (increasing or decreasing).

Taqman Real-Time RT-PCR Assay

[0277] Primers and probes were designed using Primer Express 2.0 software (Applied Biosystems, Foster City, CA). All primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). Taqman probes were labeled with reporter dye, 6-carboxy-fluorescein phosphoamidite (FAM), at the 5' end and dye quencher, minor groove binder (MGB), at the 3' end. Each 25- μ l reaction consisted of 500 nm forward primer, 500 nm reverse primer, 100 nm of Taqman probe, cDNA (20 ng of total RNA from tumor samples), and 1X (final concentration) of Taqman® One-Step RT-PCR Master Mix Reagents Kit (Applied Biosystems). The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. 18S ribosomal gene's primers and probe pairs were purchased from Applied Biosystems and used according

to manufacturer's recommendation as an endogenous control. All techniques were performed on the tissue samples according to the manufacturers' instructions.

Data analysis of Taqman assay

[0278] The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct score for genes of interest for each sample were normalized against Ct score for the corresponding endogenous control gene (18S). Relative expression of specific transcripts in the drug-treated sample compared to vehicle-treated sample was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Relative Expression} = 2^{-\Delta\Delta C_t},$$

where $\Delta\Delta C_t = (C_{t \text{ target}} - C_{t \text{ 18s control}})_{\text{drug treatment}} - (C_{t \text{ target}} - C_{t \text{ 18s control}})_{\text{vehicle treatment}}$.

2. Further Studies using Compound 1 – Results

Microarrays and RT-PCR Analysis

[0279] To identify biomarker(s), samples of tissue from the tumors were taken before and after the first dose of Compound 1. An Affymetrix GeneChip analysis of the RNA transcripts present in xenograft tissue before and after exposure to Compound 1 indicated that the levels of 28 transcripts increased and/or decreased after exposure to Compound 1 (see Table 11A and 11B). Thus, the following 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound 1: basic transcription factor 3 homologue, human c-jun proto-oncogene, human c-fos proto-oncogen, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, vinculin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, gelsolin and cyclin D2. See Figure 24 for sequences for these biomarkers.

[0280] To validate the Affymetrix GeneChip results, a subset of 11 of these 26 transcripts was chosen for quantitative RT-PCR analysis. These 11 transcripts were chosen

based on potential roles of encoded proteins. Table 13 describes the forward and reverse primers that that were designed and used in the RT-PCR experiments. The results of the quantitative RT-PCR analysis for these 11 transcripts are shown in Table 12. The RT-PCR analysis confirms the findings with the Affymetrix GeneChip analysis for these 11 transcripts.

I. EXAMPLES – ADDITIONAL STUDIES USING COMPOUND 1**1. Additional studies using Compound 1 – Materials and Methods****Human Umbilical Vein Endothelial Cells (HUVECs)**

[0281] HUVECs were obtained from Clonetics (San Diego, CA catalog# CC-2517) and were maintained in EGM media (Clonetics, catalog# CC-3121) containing EGM BulletKit (Clonetics, catalog# CC-4133: 2% Fetal Bovine Serum, 0.1% Epidermal Growth Factor, 0.1% Hydrocortisone, 0.1% Gentamicin Sulfate Amphotericin B, 0.4% Bovine Brain Extract). Cells were propagated at 37°C in a humidified atmosphere of 5% CO₂ using standard cell culture techniques. Cells were plated in 10-cm tissue culture plates at 8.5×10^5 cells/ml. After 6 hours the cells were quiesced by serum starvation overnight in starvation medium (EBM containing 0.5% FBS). DMSO (Sigma Chemicals, St. Louis, MO #D2650) or Compound 1 (to a final concentration of 10 nM, 100 nM, and 1 μ M) were added to cells. After 2 hours of exposure to Compound 1 or DMSO, VEGF₁₆₅ (R&D Systems, Minneapolis, MN; catalog# 293VE050) was added to a final concentration of 100 ng/ml; no VEGF was added to samples that are subsequently referred to as the “baseline” samples. After a 10-min, 8 hr, 24 hr and 48h VEGF stimulation the conditioned medium was filtered through 0.45 μ M syringe filter from Pall Gelman Laboratory (Ann Arbor, MI catalog# 4560) and immediately frozen on dry ice. Conditioned media was stored at –70°C until subsequent analysis.

Analysis of Conditioned Media by 2D gel electrophoresis

[0282] Thawed conditioned media samples were precipitated with three volumes of acetone for 2 hours at –20°C, then centrifuged at 13000 RPM for 15 minutes. Pellets were washed with the 2D Clean-Up Kit (Amersham, Cat. # 80-6484-51) as per protocol, air dried for three minutes, then resuspended in 8M urea (Amersham), 100 mM dithiothreitol (Fisher), 4% CHAPS (3[(cholamidopropyl)dimethylammonio]propanesulfonate from Calbiochem), and placed in a thermomixer (Eppendorf) at 600 RPM and 25°C for 2 hours. Protein was quantitated with Bio-Rad Protein Assay (cat# 500-0006) using the microassay for cuvettes protocol.

[0283] Samples were diluted to 0.3 μ g/ μ L with IEF Buffer containing 1% IPG Buffer pH 3-10 (Amersham). Eighteen centimeter IPG strips pH 3-10 (Amersham) were rehydrated with 120 μ g sample (400 μ L) under Drystrip Cover Fluid (Amersham) on the IPGphor (Amersham) at 20°C for 18 hours. Strips were focused with the following program:

200 volts for 1 hour, ramped from 200 volts to 1000 volts over two hours, held at 1000 volts for 1 hour, ramped from 1000 volts to 8000 volts over 6 hours, then held at 8000 volts for 10 hours. Polyacrylamide gels were hand cast in the Hoeffer DALT multi-gel casting chamber (Amersham) at 10% Acrylamide (Bio-Rad 40% Acrylamide Solution), 2.67% piperazine diacrylamide (Bio-Rad), 0.375 M tris, pH 8.8 (Bio-Rad), 0.075% ammonium persulfate (Bio-Rad), and 0.075% TEMED (N, N, N', N'-tetramethylethylenediamine). Gels were overlaid with water-saturated butanol (Fisher), and left to polymerize at room temperature overnight.

[0284] Focused strips were equilibrated for ten minutes with gentle shaking in 10 milliliters Equilibration Buffer: 6 M Urea (Fisher), 50 mM tris-HCl pH 8.8 (Fisher), 30% glycerol (Fisher), 2% SDS (Fisher) with 1% dithiothreitol followed by ten minutes in Equilibration Buffer with 4% iodoacetamide.

[0285] The equilibrated strips were loaded onto the gel surfaces and sealed with hot agarose overlay solution containing 0.5% agarose in 50 mM tris-HCl pH 6.8, 2% SDS.

[0286] Gels were run in the Hoeffer DALT tank (Amersham) in 25 mM tris (Fisher), 192 mM glycine (Fisher), and 0.1% SDS overnight at 100 volts and 8°C.

[0287] The gels were washed three times in 500 mL Fixative (10% methanol and 7% glacial acetic acid) for one hour each with gentle agitation. The gels were then stained overnight in 500 mL Sypro Ruby Protein Gel Stain (Molecular Probes). Gels were again washed three times in 500 mL fixative for an hour each with gentle agitation. Images were obtained on the Fluor S MultiImager (Bio-Rad) using transilluminated ultraviolet light for 45 seconds with the 520LP emission filter. Image analysis was done using PDQuest version 7.0.1 (Bio-Rad).

2D Gel Spot Cutting

[0288] The automated gel cutting was performed using the ProteomeWorks Spot Cutter (BioRad, Hercules, CA) and PDQUEST (v.7.0.1) software. Three sets of 2D gels were cut (Table 14). Based on the gel imaging analysis, the same spots of all three gels were combined in the same well of a 96-well plate.

Protein In-gel Digestion

[0289] The automated digestion was performed using Investigator ProGest Digestion Station (Genomic Solutions). The sample plate (96-well pink plate) was placed onto the reaction block. A white sample collection plate was placed onto the collection block. The method used, Ruby48proGestv1, was based on the software ProGest Method Editor (v.1.1.0.29). Then the samples were digested automatically with trypsin (0.19 µg/well) at 37 °C for overnight.

MALDI-TOF-MS Analysis

[0290] After in-gel digestion, the digest was concentrated and desalted by using C18 reversed phase Ziptip (Millipore, Bedford, MA). Bound peptides were eluted with 4 µL matrix solution (α-cyano-4-hydroxycinnamic acid in acetonitrile/0.1%TFA 1:1 v/v).

[0291] 1 µL eluted solution was spotted onto the MALDI target. Peptide mass mapping was performed on an ABI Voyager STR matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometer (Applied Biosystems, Framingham, MA). The acceleration voltage was 20 kv, the grid voltage was 14kv, the extraction delay time was 300nsec, external calibration during mass spectrometry data acquisition was used. The acquired peptide mass mapping spectra was processed and analyzed by Data Explorer software (Version 4.0.0.0.). The internal calibration was performed by using trypsin autolysis peptide mass 842.5099 and 2211.1046.

MALDI-MS/MS Analysis

[0292] The MALDI-MS/MS analysis was performed using API Qstar Pulsar equipped with oMALDI Source (PE Sciex). The curtain gas was 25, the declustering potential was 45, the focusing potential was set from range 220 to 250 V various by samples. CAD gas was 7 and collision energy was at 35 to 100 depending on samples. The ion energy was set at 1 kV. Data acquisition and processing was done using Analyst QS and oMALDI Server (v. 2.2) softwares. The biomarker identification was obtained with MASCOT database search using MS/MS spectra. The publically accessible link to the "MASCOT" tool for protein identification using peptide data is:

<www.matrixscience.com/cgi/index.pl?page=/search_form_select.html>.

ELISA Analysis

[0293] Reagents for human pro-Matrix Metalloproteinase 1 (pro-MMP-1) ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN; catalog # DMP100). ELISAs were performed on conditioned media samples according to the manufacturers' instructions. The optical density of each well was determined using a universal microplate spectrophotometer (μ Quant) from Bio-Tek Instruments, Inc. (Winooski, VT). KC-4 software from Bio-Tek Instruments, Inc. was used to extrapolate cytokine concentrations from the standard curves.

2. Additional studies using Compound 1 – Results**2D Gel Analysis of Conditioned Media from VEGF +/- Compound 1 Treated HUVECs.**

[0294] Conditioned media isolated from HUVECs pre-treated with vehicle (DMSO) or Compound 1 (1 μ M) and subsequently stimulated with VEGF for 24 and 48 hours or baseline, untreated samples were analyzed by 2D gel analysis (see Materials and Methods). This analysis identified 1 spot (#1202) whose abundance consistently increased with addition of VEGF in two separate gel runs and appeared to decreased with Compound 1 pre-treatment, although not consistently using this technology (Table 15). These spots were excised and underwent MALDI and MALDI-MS/MS analysis for subsequent protein identification.

Identification of Interstitial Collagenase Precursor/pro-MMP1 By Database Search Based On Peptide Mass Fingerprint Spectra.

[0295] Peptide mass fingerprint data sets were analyzed by searching SwissProt protein database with ProteinProspector MS-Fit (Version 3.2.1). The searches were set with the following parameters, Human Mouse (Species), 1-66 kDa (molecular weight range), trypsin used for digest, maximum one missed cleavage, mass tolerance 50 ppm. Methionine was set as modified by oxidation and cysteine was set as modified by carbamidomethylation. Peptides were considered with hydrogen at N terminus and free acid at C terminus. The peptide masses were monoisotopic. The database search result was significant if the protein was ranked as the first hit and the sequence coverage was more than 30%, in addition a MOWSE score higher than 1e+003 (MS-Fit) was required. As summarized in Table 16 and

Table 17, Spot 1202 was definitively identified as interstitial collagenase precursor (pro-MMP1).

ELISA Analysis of pro-MMP1 Levels in HUVEC Conditioned Media

[0296] Because the quantitation of pro-MMP1 levels in 2D gels is only semi-quantitative (and therefore less consistent), the levels of pro-MMP-1 in HUVEC conditioned media were also assayed using a quantitative ELISA assay. The ELISA analysis indicated that levels of pro-MMP1 increase quantitatively when HUVEC cells are treated with VEGF and are decreased with pre-incubation of Compound 1 at 10nM, 100nM or 1uM concentrations (Table 18).

Pro-MMP1 Levels in Plasma from Compound 1 Treated Patients in Study B

[0297] Pro-MMP1 levels in the plasma of Study B patients after treatment with Compound 1 (day 1 pre-treatment, day 1 24 hr post-treatment, day 13 pre-treatment, day 13 12 hr post-treatment, and day 13 24 hr post-treatment) was analyzed. The results (see Table 19) demonstrate that pro-MMP1 levels increased in the plasma of patients after they received Compound 1.

J. EXAMPLES – MORE STUDIES USING COMPOUND 1**1. More studies using Compound 1 – Materials and Methods****Plasma Samples**

[0298] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site.

[0299] Plasma samples were then thawed and centrifuged to remove particulate matter (10 min @ 5000 x g). The resulting supernatants were collected and split into aliquots and were re-frozen at –80 °C. Prior to assay, samples were thawed, Immunoglobulin Inhibiting Reagent (IIR, Bioreclamation Inc) was added to a final concentration 0.25 mg/mL, and Tween 20 was added to final concentration of 0.1%.

Antibody chip microarray manufacture

[0300] Glass slides were cleaned and derivatized with 3-cyanopropyltriethoxysilane. The slides were equipped with a Teflon mask, which divided the slide into sixteen 0.65 cm diameter wells or circular analysis sites called subarrays. Printing was accomplished with a Perkin-Elmer Spotarray Enterprise non-contact arrayer equipped with piezoelectric tips, which dispense a droplet (~350 pL) for each microarray spot. Antibodies were applied at a concentration of 0.5 mg/mL at defined positions. Each chip was printed with sixteen copies of one type of array, either Array 1.1 or Array 2.1 (see below). Both arrays consist of capture antibodies against different analytes and are defined by the antibody set contained. Analytes measured using both arrays are listed in Table 20.

Array 1.1 detector set.

Analyte	Name
ANG	Angiogenin
BLC (BCA-1)	B-lymphocyte chemoattractant
EGF	Epidermal growth factor
ENA-78	Epithelial cell-derived neutrophil-activating peptide
Eot	Eotaxin
Eot-2	Eotaxin-2
Fas	Fas (CD95)
FGF-7	Fibroblast growth factor-7
FGF-9	Fibroblast growth factor-9
GDNF	Glial cell line derived neurotrophic factor
GM-CSF	Granulocyte macrophage colony stimulating factor
IL-1ra	Interleukin 1 receptor antagonist
IL-2 sR α	Interleukin 2 soluble receptor alpha
IL-3	Interleukin 3
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IL-13	Interleukin 13
IL-15	Interleukin 15
MCP-2	Monocyte chemotactic protein 2
MCP-3	Monocyte chemotactic protein 3
MIP-1 α	Macrophage inflammatory protein 1 alpha
MPIF	Myeloid progenitor inhibitory factor 1
OSM	Oncostatin M
PIGF	Placental growth factor

Array 2.1 detector set.

Analyte	Name
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AR	Amphiregulin
BDNF	Brain-derived neurotrophic factor
FLT-3 Lig	fms-like tyrosine kinase-3 ligand
GCP-2	Granulocyte chemotactic protein 2
HCC4 (NCC4)	Hemofiltrate CC chemokine 4
I-309	I-309
IL-1 α	Interleukin 1 alpha
IL-1 β	Interleukin 1 beta
IL-2	Interleukin 2
IL-17	Interleukin 17
MCP-1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony stimulating factor
MIG	Monokine induced by interferon gamma
MIP-1 β	Macrophage inflammatory protein 1 beta
MIP-1 γ	Macrophage inflammatory protein 1 delta
NT-3	Neurotrophin 3
NT-4	Neurotrophin 4
PARC	Pulmonary and activation-regulated chemokine
RANTES	Regulated upon activation, normal T expressed and presumably secreted
SCF	Stem cell factor
sgp130	Soluble glycoprotein 130
TARC	Thymus and activation regulated chemokine
TNF-RI	Tumor necrosis factor receptor I
TNF- α	Tumor necrosis factor alpha
TNF- β	Tumor necrosis factor beta
VEGF	Vascular endothelial growth factor

Microarray Chip Physical Quality Measures

[0301] Each print run of microarray chips was assigned a unique Production Sheet Number, and the RCAT immunoassay run for this print run was documented. For each print run, printed slides were subjected to the following control measures: (1) two slides, one from the start and one from the end of the run, were inspected

using light microscopy. If the percentage of missing spots observed was greater than 5%, then the batch failed and the slides were discarded immediately. For all print runs described herein, 100% of the printed spots were present on slides selected for this examination; and (2) for each print run, two of the printed slides were examined by a Cy5-labeled goat-anti-mouse antibody (GAM-Cy5). Since the majority of capture antibodies in these arrays were of mouse origin, this procedure examined total antibody attachment and provided a rapid measure of surface and binding uniformity. To account for differences in binding efficiency for different capture antibodies, the intensities of all spots for each individual capture antibody were measured across the chip (4 spots/subarray, 64 spots/chip) and a %CV was calculated for that feature. The average of these %CVs for all quantified capture antibodies must be below 20% for the print batch to pass. Chips treated with GAM-Cy5 were also checked for missing spots after the assay and if the percentage of missing spots was greater than 5%, then the batch failed (for these studies 100% of the printed spots were still present after this assay). Following these QC measures, qualified slides were stored at 4°C until used.

Reagent Quality Control Measures

[0302] The assay suite was considered as consisting of the microarray chips, detector antibodies and the reagents required for the RCAT portion of the assay. There were validation procedures for these reagents individually as well as a functional validation of the entire set. Reagents used in the RCA portion of the assay were from reserved vendor lots where possible. Materials produced in-house were subjected to QC procedures and qualified on microarray chips before release. If lot numbers changed for a particular reagent that is supplied by an outside vendor, the new lots were qualified by comparison with existing qualified stocks.

[0303] For each array type, a concentrated batch of detectors was prepared which consisted of a mixture of biotinylated antibodies directed against all analytes represented by an array. A functional QC was then performed for each detector antibody batch by carrying out the standard RCAT assay on a specially prepared sample set. Mixtures of 2-3 different cytokines were prepared so as to provide a high intensity signal and applied to 14 wells of a chip (with each well being treated with a different mixture up to the total complement of detector antibodies) and two arrays

were used as blank controls. The chips were developed and scanned and the resulting signals were compared to the positional map of the particular array. This examination demonstrated that the stock detector mixture was complete and the features were active. Once a detector batch had passed this QC, it was distributed into smaller volumes and released for use in the assay.

Positional and Functional Quality Measures

[0304] Following printing, a set of microarray chips was validated in concert with the qualified reagents discussed above. This was a two-part quality control measure. The first portion was identical to the detector antibody qualification procedure just described. In this case, the high intensity signals were compared to the array map and the proper positioning of capture antibody replicates was verified. The second test was a functional QC for all analytes of a specified array using known sample matrices. Normal human serum (Jackson ImmunoResearch Laboratories, Code#009-000-121) and heparinized plasma were assayed neat or spiked with purified recombinant cytokines representing all analytes in the array. Spiked mixtures were then titrated down the subarrays of a slide from 5,000 pg/ml to 20 pg/mL of spiked cytokine concentrations along with three subarrays for each un-spiked control sample. The data was quantified and for every analyte in the array a titration curve was generated to show that the feature intensity was above background and exhibiting increasing intensity with increasing analyte concentrations.

RCA Immunoassay

[0305] Prior to assay, the slides were removed from storage at room temperature in sealed containers and opened in a humidity controlled chamber (35-40%). Blocking was done by submerging the slides in a Coplin jar filled with blocking buffer (Seablock, Pierce Chemical Co., 1:1 dilution with 1X PBS) pre-chilled to 4°C, and placing the Coplin jar in a 37°C incubator for 1 hour. The slides were then washed twice (2 min per wash) in 60 mL of 1x PBS/0.5% Brj-35 washing buffer. On each slide, control serum (Jackson ImmunoResearch Laboratories) was applied to one subarray, plasma control applied to two subarrays, and a negative control with PBS buffer applied to two subarrays. The test samples were assayed on the remaining 11 subarrays. Twenty microliters of the treated sample were then

applied to each subarray. The basics of performing immunoassays with RCA signal amplification has been described (*Nat. Biotechnol.* (2002) 20:359-65) and we are using SOPs derived from the protocols used in that study. Slides were scanned (GenePix 4000B, Axon Instruments Inc.) at 10 μm resolution with a laser setting of 100% and a PMT setting of 550 V. Mean pixel fluorescence values were quantified using the fixed circle method in GenePix Pro 4.0 (Axon Instruments). Using proprietary software, the fluorescence intensity of microarray spots was analyzed for each feature and sample, and the resulting mean intensity values were determined. Dose-response curves for selected cytokines were examined, ensuring that feature intensity is above background and exhibiting increasing intensity with increasing analyte concentration.

ELISA Analysis

[0306] Reagents for FLT3 ligand (FL) and IL-6 ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN; catalog #s DFK00, Q6000). C-reactive protein (CRP) (accession ID AAA 52075) ELISA kits were obtained from KMI Diagnostics (Minneapolis, MN; catalog #EU59131). ELISAs were performed on patient plasma according to the manufacturers' instructions. The FL and CRP kits relied on a colorimetric readout; the optical density of each well was determined using a microplate spectrophotometer and data was analyzed using KC-4 software from Bio-Tek Instruments, Inc. The IL-6 kit was a chemiluminescent sandwich ELISA; luminescence values were determined on a microplate luminometer. SOFTmaxPRO software was used to extrapolate cytokine concentrations from the standard curves.

2. More studies using Compound 1 – Results

Plasma markers identified using Antibody chip technology

[0307] A multiplex antibody chip based approach (MSI, Molecular Staging Inc.) was used to identify plasma biomarkers of compound 1. Plasma samples harvested from 3 advanced malignancy patients pre and post Compound 1 treatment (Phase I trial A) were used for this analysis. Twenty three of 108 markers tested, showed changes following Compound 1 treatment (day 28). These are listed in Table 21. Controls included normal donor plasma which did not show significant changes

in these markers. Each of these is a potential biomarker of Compound 1, and may reflect drug exposure, biological activity or efficacy.

[0308] A number of markers showing the most dramatic changes and/or of known biological significance were further investigated (specifically VEGF, PLGF, IL-6, IL-8 and MCP-1). The relative changes were validated by ELISA on the same patient samples assessed in the antibody chip screen, and both methods showed good concordance (Table 22). Several of these markers had previously been identified by ELISA analysis on compound 1 treated samples, (PLGF, VEGF, IL-6), and several were novel (FLT3 ligand and MCP-1). Additional data on FLT3 ligand levels tested in an expanded set of patients is provided in Figure 25. Dramatic induction was observed following Compound 1 treatment in all cases.

Plasma ELISA Studies

[0309] In an effort to identify novel biomarkers of exposure to Compound 1, plasma samples were analyzed from 18 patients enrolled in Trial B. Plasma was taken both before study (D1 PRE) as well as at the end of the first cycle of treatment (Day 28 POST). Each time point was measured in triplicate and the standard deviation from the mean was calculated. Both the mean value and standard deviation for each patient at each time point is shown graphically in Figure 25. It was found that 100% of the patients exhibited an increase in FLT3 ligand (FL) concentration from day 1 to day 28. In 14 out of 18 patients, the increase was more than four-fold. The increase in FLT3 ligand concentration is attributed to treatment with Compound 1.

Plasma ELISA Studies – Fatigue Corrolation

[0310] To find biomarkers that correlated with fatigue, plasma samples were analyzed from 62 patients enrolled in trials for Compound 1. Samples were taken before study (D1) and either two or four weeks after the start of cycle 1 dosing (Day 13 for trials B, C and D and Day 28 for A and E). The patients are grouped according to their highest recorded fatigue grade (0-4 scale from the NCI Common Toxicity Criteria). As seen in Figure 26, there is a statistically significant difference between the increases in IL-6 seen in patients with low fatigue (Grade 1 or 0) and those with

moderate to high fatigue (Grade 3 or 4), $p=0.001$. Thus, a patient who exhibits a large change in IL-6 plasma concentration (greater than two-fold) after treatment with Compound 1 has a much higher chance of experiencing a high degree of fatigue (Grade 3 or 4) than a patient whose IL-6 level remains more stable.

[0311] Plasma samples were further analyzed from 18 patients enrolled in Trial B for Compound 1. Samples were taken before study (D1) and two weeks after the start of cycle 1 dosing (D13). As shown with IL-6 levels, the patients are grouped according to their highest recorded fatigue grade (0-4). See Figure 27. It was determined there is a statistically significant difference in C-reactive protein (CRP) (accession ID AAA 52075) induction between patients with little fatigue (Grade 0, 1, or 2) and those with moderate to severe fatigue (Grade 3 or 4), $p = 0.0088$. Therefore, patients with a greater than two-fold increase in C-reactive protein after treatment with Compound 1 are more prone to experiencing high fatigue than those who have smaller fold changes in CRP.

Plasma ELISA Studies –Corrolation to biological response and/or clinical efficacy

[0312] Levels of C-reactive protein were measured as described above for the experiments involving CRP and fatigue. ELISAs were performed on plasma samples from patients before treatment (i.e., baseline values). The patients' samples and results were divided into two groups based upon observed clinical outcome. Patients with stable disease (SD pts) were defined as patients on study for over 6 months. Patients with progressive disease (PD pts) were defined as patients who had come off study due to disease progression or lack of efficacy in fewer than 6 months. This separation of patients demonstrated that patients with progressive disease had much higher baseline levels of CRP than those patients who were stable (median values of 63.8 $\mu\text{g/mL}$ vs. 6.5 $\mu\text{g/mL}$, respectively) (Figure 28). If a patient were to have a baseline level of CRP of above 20 $\mu\text{g/mL}$ before treatment, that patient has a greater chance of rapidly progressing than if the level of CRP were below 20 $\mu\text{g/mL}$. Thus, CRP is a baseline marker of biological response and/or clinical efficacy.

K. EXAMPLES – COMPOUND 1 STUDIES OF OB-CADHERIN 1 PROTEIN**1. Compound 1 studies of OB–cadherin 1 protein – Materials and Methods****Tumor samples**

[0313] Colo205 human colon xenograft tumors were isolated and fixed in Streck Tissue Fixative (Streck Laboratories, Inc., La Vista, NE). Samples used in immunohistochemistry were sent out to BioPathology Sciences Medical Corporation (South San Francisco, CA) for paraffin embedding and sectioning.

Antibodies

[0314] A rabbit polyclonal antibody recognizing the cytoplasmic tail region of OB-cadherin 1 (cadherin 11) was purchased from Zymed Laboratories, Inc. (Zymed reagent #71-7600; South San Francisco, CA).

Immunohistochemistry

[0315] Sections (4-5 μ m) stained using an automated immunohistochemistry system (Benchmark System, Ventana Medical Systems, Inc., Tucson, Arizona). In brief, slides were deparaffinized using heat at 75°C and Ventana's EZ Prep product (Ventana reagent #950-102). Antigen retrieval was performed by incubating the slides for 30 min with Ventana's CC2 product (Ventana reagent #950-123), a citrate-based solution with pH 6.0. Primary antibody (5 μ g/ml) was incubated for 24 min at room temperature, followed by a secondary detection system, using biotinylated secondary antibody (Vector anti-rabbit secondary, BA-1000, at 2.5 μ g/ml; Vector Laboratories, Burlingame, CA) with incubation time of 8 min. Streptavidin-horseradish peroxidase with 3, 3' diaminobenzidine as a substrate were used in conjunction with the secondary detection system. All samples analyzed for OB-cadherin 1 expression were also stained with the omission of primary antibody as a negative control.

2. Compound 1 studies of OB-cadherin 1 protein – Data Summary

[0316] As expression of OB-cadherin 1 (cadherin 11) RNA was found to be up-regulated at 24 hour post-Compound 1 treatment (see Table 12), effects on OB-cadherin 1 expression at the protein level was also examined. Colo205 xenograft tumors were isolated from Compound 1-treated mice at 24 and 48 hours post treatment. Tumors were fixed in formalin and sections were isolated and processed for immunohistochemistry (IHC).

[0317] Tissue sections were stained with an antibody that recognizes OB-cadherin 1. As a negative control, adjacent sections were processed similarly but with the omission of a primary antibody. This analysis identified up-regulation of OB-cadherin 1 protein in Colo205 tumors treated with Compound 1 for 24 and 48 hours as compared to vehicle treated samples (Figure 29).

TABLES**Table 1.**

	Number of samples from which RNA was processed	Number with RNA yield >1ug, at both d1 and d56	Number hybridized to U95A chips	Number for which data passed Quality Control inspection for further analysis
SU5416				
CR	0	0	0	0
PR	13	8	6	6*
MR	6	3	2	1
SD	6	5	1	1
PD	10	7	6	5*
Control				
CR	1	1	1	1*
PR	9	5	5	5*
MR	4	1	1	0
SD	3	2	2	2
PD	11	9	7	6*
Total:	63	41	31	27

*** These samples were included in the dataset used in detailed analysis**

Table 2.

<u>Affymetrix number</u>	<u>Gene name/ Symbol</u>	<u>Putative function(s)</u>	<u>Increased in SU5416 arm</u>	<u>Increased in Control arm</u>
34546_at	Defensin α 4	Corticostatic, Ca channel regulator	10 of 11	6 of 12
33530_at	CEA CAM 8	Tumor antigen, integral membrane protein.	9 of 11	4 of 12
37054_at	BPI	Anti-pathogen response	9 of 11	4 of 12
31859_at	MMP-9	Protease; ECM maintenance	8 of 11	2 of 12
32821_at	Lipocalin 2	Anti-pathogen response; apoptosis	10 of 11	5 of 12
34319_at	S100 P	Ca-binding protein	9 of 11	3 of 12
41249_at	Hypothetic. Protein FLJ13052	unknown	7 of 11	1 of 12
1962_at	Liver arginase	Amino acid metabolism	9 of 11	3 of 12
266_s_at	CD24 antigen	Anti-pathogen response; differentiation of B cells	9 of 11	0 of 12
31506_s_at	Defensin α 3	Chemotaxis; anti-microbial response	10 of 11	4 of 12
32275_at	Antileuko-protease	Secreted inhibitor of serine proteases	9 of 11	4 of 12
115_at	Thrombospondin 1	Blood clotting; angiogenesis	9 of 11	3 of 12
37149_s_at	Lactoferrin	Iron transport; putative protease	11 of 11	5 of 12

Table 3.

<u>Gene</u>	<u>Forward Primer</u>	<u>Reverse Primer</u>
Thrombospondin 1	TTGGCTACCAGTCCAGCAGC (SEQ ID NO: 1)	GGGTTGGTGTCCCAGTAGGA (SEQ ID NO: 2)
MMP-9	CCCGGAGTGAGTTGAACCA (SEQ ID NO: 3)	CCTAGTCCTCAGGGCACTGC (SEQ ID NO: 4)
Defensin α 3	CCCAGAAGTGGTTGTTTCCT (SEQ ID NO: 5)	GTCCATGTTTTTCCTTGAGCCT (SEQ ID NO: 6)
Lactoferrin	CTGGAAGCCTGTGAATTCC (SEQ ID NO: 7)	GAATGGCTGAGGCTTTCTTGG (SEQ ID NO: 8)
Lipocalin-2	GCTGACTTCGGAACATAAAGGAGAA (SEQ ID NO: 9)	TGGGACAGGGAAGACGATGT (SEQ ID NO: 10)
CD24	CTGCCTCGACACACATAAACCTT (SEQ ID NO: 11)	CATCTAAGCATCAGTGTGTGACC A (SEQ ID NO: 12)

Table 4.

<u>P-value of Mann-Whitney U Test</u>		
<u>Gene</u>	<u>Affymetrix</u> (n = 23)	<u>SYBR Green RT-PCR</u> (n = 31)
MMP-9	0.0025	0.0748
Thrombospondin 1	0.0267	0.7186
CD24	0.0006	0.0057
Defensin α 3	0.0002	0.2196
Lactoferrin	0.0002	0.0065
Lipocalin-2 (LCN2)	0.0005	0.0057

Table 5.

Gene	n	Rank Sum (Treatment)	Rank Sum (Control)	Mann-Whitney U	p-value
MMP-9	36	415	251		0.0095
CD24	36	443	223		0.0005
Lactoferrin	36	460	206		0.0001
LCN2	36	419	247		0.0065

Table 6.**Predictor Gene Set for discriminating between the control and Compound B arms: LCN2, CD24, Lactoferrin**

1. All cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	6	30	83
Total	32	35	84

2. Jackknifed classification matrix for all cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	8	28	78
Total	34	33	81

3. Prediction subset (randomly selected 34 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	13	1	93
Treatment	4	16	80
Total	17	17	85

4. Validation subset (randomly selected 33 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	11	6	65
Treatment	5	11	69
Total	16	17	67

Table 7.

Trial C patients 1-23 PLGF plasma level ratios

<u>Patient #</u>	<u>d1 (6 hr):d1 (0 hr)</u>	<u>d29:d1</u>	<u>d42:d1</u>
1	0.695512	1.871238	0.398897
2	2.050289	11.96579	1.040025
3	1.965517	3.586207	1.206897
4	1.985061	24.72922	1.985061
5	1.09557	11.3316	1.09557
6	1.800672	11.02117	1.365586
8	1.16493	12.38985	1.157115
10	1.622462	>10	2.652309
11	1.250022	7.511615	1.386382
13	1.038442	1.817441	NA
15	0.896403	6.651554	1.189041
17	0.907692	19.21308	1.134385
18	1.007357	12.30822	1.105295
20	1.2261	11.29078	1.598445
21	1.518564	14.84205	0.955559
22	1	2.423462	0.815385
Average	1.326537	10.19689	1.272397

***Note: d15:D1 ratio is 6.4 for pt. 13

Table 8.

<u>MIG</u>					<u>IP-10</u>		
<u>Patient</u>	<u>day 1</u>	<u>day 15</u>	<u>end C1 dosing</u>	<u>Ratio</u>	<u>day1</u>	<u>end C1 dosing</u>	<u>Ratio</u>
11 (B)	41.927		739.71	17.64281	55.617	>500	>9
1	48.375		1066.2	22.04031	64.847	>500	>7.7
11	34.432		344.93	10.01772	65.32	384.06	5.879669
17	166.8		907.09	5.438189	72.29	>500	>6.9
24	80.751		314.2	3.890973			
26	80.751		995.47	12.32765	64.296	>500	>7.7
27	80.826		81.439	1.007584			
7	106.04		145.64	1.373444	139.2	240.31	1.726365
20	161.91		698.23	4.312458	73.67	>500	>6.9
22	37.685	339.16		8.999867			
9 (A)	60.393		138.56	2.294306			

<u>I-TAC</u>				
<u>Patient</u>	<u>day 1</u>	<u>day 15</u>	<u>end C1 dosing</u>	<u>Ratio</u>
11 (B)	428.83		>4000.0	>9
1				
11				
17				
24	259.38		771.04	2.972627
26	97.917		701.46	7.163822
27	139.94		315.69	2.255895
7				
20				
22	190.76	2020.2		10.59027
9 (A)	59.975		212.26	3.539141

Table 9.

<u>Patient #</u>	<u>PLGF Ratio (end dosing:d1)</u>	<u>VEGFR2 ratio (end dosing:d1)</u>	<u>Primary Diagnosis</u>
Trial C			
1	1.871237941	0.265856292	Synovial Sarcoma
2	11.96579454	0.25171334	Rectal
3	3.586206897	0.5673112	Gall-bladder
4	24.72921991	0.34236691	Hepatocellular
5	11.33159926	0.406890612	Melanoma
6	11.02116835	0.572980623	Breast
7	23.86685363	0.404286499	Ovary
8	12.38984817	0.318366334	Small Cell Lung
10	10	0.45614753	Melanoma
11	7.511615487	0.323681006	Met. Colon
13	1.817440506	0.460416464	Renal Cell Carcinoma
14	3.080408542	0.575703582	Met. Melanoma
15	6.651553529	0.506347193	Renal Cell Carcinoma
17	19.21307692	0.177452364	NSCLC
18	12.30822285	0.271285002	NSCLC
20	11.29078149	0.385479698	Colon
21	14.84205128	0.369637606	Breast
22	2.423461538	0.479139734	Sarcoma
23	1	0.504789782	Sarcoma
24	0.99016936	0.457140878	met. Rectal carcinoma
25	12.03862173	0.250133543	Retropero Sarcoma
26	13.29469461	0.493391074	Met Pelvis Sarcoma
29	5.237072177	0.59927457	SCCR R) Parotid
30		0.519969363	Colon AdenoCA
31		0.330647033	Lung AdenoCA
Trial A			
1		0.565173104	Renal Cell Carcinoma
3		0.597994214	Bronchial adeno.
4		0.685465839	breast carcinoma
5	12.97391648	0.182557005	uterine
6	25.082632	0.458079657	pelvic angiosarcoma
7		0.648790016	pleural mesothelioma
8		0.64392508	uterine
9		0.38520981	Bronchial adeno.
10	5.301660143	0.44915001	colorectal
13		0.297438475	neuroendocrine

Table 9. cont.

<u>Patient #</u>	<u>PLGF Ratio (end dosing:d1)</u>	<u>VEGFR2 ratio (end dosing:d1)</u>	<u>Primary Diagnosis</u>
Trial D			
1		<i>0.502083475</i>	GIST
3	2.98130415	<i>0.670742516</i>	GIST
4	<i>5.228142589</i>	0.972905837	GIST
5	1.351061278	<i>0.616277438</i>	GIST
6	<i>7.055260831</i>	<i>0.684932856</i>	GIST
13	<i>4.095209935</i>	<i>0.600072917</i>	GIST
14	<i>4.786806356</i>	<i>0.685754939</i>	GIST
15	<i>22.29951691</i>	0.767346939	GIST
16	<i>3.034877351</i>	0.727153597	GIST
18	<i>16.89889246</i>	<i>0.471077781</i>	GIST
19	2.782095462	<i>0.542935245</i>	GIST
20	<i>12.47129736</i>	<i>0.598602839</i>	GIST
21	<i>11.56450225</i>	<i>0.351218422</i>	GIST
22	2.996492067	<i>0.644054653</i>	GIST
Trial B			
4		<i>0.67109839</i>	Head & Neck
5		<i>0.678411145</i>	CRC
6		<i>0.4130696</i>	thymic
7		<i>0.301532905</i>	CRC
8		<i>0.456886687</i>	thyroid
9		<i>0.597322954</i>	thyroid

Table 10.

<u>MIG</u>					
<u>Patient #</u>	<u>day 1</u>	<u>day 15</u>	<u>end C1 dosing</u>	<u>Ratio</u>	<u>Cancer Type</u>
11 (B)	41.927		739.71	17.64281	Pancreatic
1	48.375		1066.2	22.04031	Synovial Sarcoma
11	34.432		344.93	10.01772	Met. Colon
17	166.8		907.09	5.438189	NSCLC
24	80.751		314.2	3.890973	Met. Rectal
26	80.751		995.47	12.32765	Pelvis Sarcoma
20	161.91		698.23	4.312458	Colon
22	37.685	339.16		8.999867	Sarcoma
9 (A)	60.393		138.56	2.294306	Bronchial Adeno.

Table 11A.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Increase
Basic transcription factor 3 homologue	Transcription factor	M90354	6	2.1
c-jun proto oncogene	Transcription factor	J04111	6	2.5
c-fos cellular oncogene	Transcription factor	K00650	6	4.2
Tyrosine phosphatase non-receptor type 2	Protein phosphatase	NM_080422	6	2.2
cdc2-related protein kinase	Cell cycle regulation	M68520	6	19
Cyclin C	Cell cycle regulation	M74091	6	2.5
DNA polymerase gamma	DNA polymerase	U60325	6	7.3
Basic transcription factor 3 homologue	Transcription factor	M90354	24	2.2
Protein kinase C alpha	Protein kinase	X52479	24	3.0
Lipocortin II/annexin A2	Ca ⁺⁺ -regulated membrane binding protein	D00017	24	2.3
Histone H2B, member R	Transcriptional regulation	AF531293	24	3.0
Amphiregulin	Growth factor	NM_001657	24	6.1

Table 11A cont.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Decrease
Ephrin receptor EphB4	Tyrosine kinase receptor	NM_004444	6	2.5
Hanukah factor/Granzyme A	Serine protease	M18737	24	2.3
von Hippel-Lindau (VHL) tumor suppressor	Tumor suppressor	NM_000551	24	3.7
OB-cadherin 1	Ca ⁺⁺ -dependent cell adhesion protein	D21254	24	2.2
OB-cadherin 2	Ca ⁺⁺ -dependent cell adhesion protein	D21255	24	2.0
Phosphoinositol 3-phosphate-binding protein-3 (PEPP3)	Phosphoinositide-binding protein	NM_014935	24	2.1
Phosphoinositol 3-kinase, p85 subunit	Proliferation	M61906	24	2.2
Mucin 1	Adhesion, cell-cell interaction	J05582	24	2.5
Hepatitis C-associated microtubular aggregate p44	Interferon-induced protein	Exon 1-9 D28908, D28909, D28910, D28911, D28912, D28913, D28914, D28915	24	2.0
ErbB3/HER3 receptor tyrosine kinase	Growth factor receptor	M29366	24	2.1

Table 11B.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Increase
Vinculin	Cell adhesion	M33308	4	2.5
Basic transcription factor 3	Transcription factor	M90357	24	2.2
Phosphoinositol 3-kinase, p110 subunit	Proliferation	NM_006219	24	4.5
Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Decrease
Gelsolin	Actin binding protein	X04412	4	2.1
Cyclin D2	Transcription	NM_001759	4	2.2

Table 12.

Transcript Name	Accession No.	Relative Expression Level (6 hr)	Relative Expression Level (24 hr)
Amphiregulin	NM_001657	1.9	2.5
Cdc2-related protein kinase	M68520	0.43	0.55
Phosphoinositol 3-kinase, p110 subunit	NM_006219	0.59	1.6
Cyclin C	M74091	842	223
OB-cadherin 1	D21254	0.35	23.8
OB-cadherin 2	D21255	0.40	0.51
Phosphoinositol 3-kinase, p85 subunit	M61906	1.0	230
Mucin 1	J05582	0.32	1.13
von Hippel-Lindau tumor suppressor	NM_000551	0.9	0.55
Ephrin receptor, EphB4	NM_004444	3.5	3.1
Gelsolin	X04412	4.0	0.04

Table 13.

Transcripts	GenBank Accession No.	Forward Primer (5' - 3')	Reverse Primer (5' - 3')	Taqman Probe (5' - 3')
Amphiregulin	NM_001657	ATGATGAGTCGTCCTCT TTCC (SEQ ID NO: 13)	TGACAATTGAAAGTTTAA AACCATCAT (SEQ ID NO: 14)	TCCATTGTCTTATGA TCCAC (SEQ ID NO: 15)
CDK-2 related protein	M68520	AGTTAGAAAGTTAGGGTTT AGGCATCAAT (SEQ ID NO: 16)	TACCCATGCCCTCACTCA ATC (SEQ ID NO: 17)	AAGTGTGAGCAATTCT CAA (SEQ ID NO: 18)
PI3-kinase, p110	NM_006219	CCAGTGTGTGAGGATGC ATATC (SEQ ID NO: 19)	CAGTCAACATCAGCGCAA AGA (SEQ ID NO: 20)	ATTCCCATGCCGTCG TA (SEQ ID NO: 21)
PI3-kinase, p85	M61906	CAAACCTACTGTATCTCT AATACAGTGTGACT (SEQ ID NO: 22)	GACAGAGATGATTATCCC TTTAAACCA (SEQ ID NO: 23)	AGCGCTCACCTTTG (SEQ ID NO: 24)
Cyclin C	M74091	CCTACAGACAGACATACA TAGACATTCAA (SEQ ID NO: 25)	ATTATGCTTCATGTTTCCT GGCTTA (SEQ ID NO: 26)	CCAAATTAAGAAAT ATTATACTAATCA (SEQ ID NO: 27)
OB-cadherin 1	D21254	GACAACAGTTCTGAGCTG TAATTTCG (SEQ ID NO: 28)	TGGGTTAAAGCTGGCTGA ATATTAT (SEQ ID NO: 29)	ACTCTGGACACTCTA TATGT (SEQ ID NO: 30)
OB-cadherin 2	D21255	TCAGCCAGCTTAAACCCA TACAA (SEQ ID NO: 31)	TGGCACGTATTAGTTAA GATGAAAGTAG (SEQ ID NO: 32)	CTTGTTACTGCTGAT TCT (SEQ ID NO: 33)
Mucin 1	J05582	TTCAGAGGCCCCACCAAT T (SEQ ID NO: 34)	CCCACATGAGCTTCCACA CA (SEQ ID NO: 35)	TCTCGGACACTTCTC (SEQ ID NO: 36)

Table 13 cont.

Transcripts	GenBank Accession No.	Forward Primer (5' - 3')	Reverse Primer (5' - 3')	Taqman Probe (5' - 3')
VHL tumor suppressor	NM_000551	TGAGGCAGGGACAAAGTCT TTCT (SEQ ID NO: 37)	ACCCTGACTGAAGGCTCA TGA (SEQ ID NO: 38)	CTCTTTGAGACCCCA GTGC (SEQ ID NO: 39)
EphB4	NM_004444	TCTACCGTCCTTGTCATA ACTTTGTG (SEQ ID NO: 40)	ATGATGATGGGGCCCTGT T (SEQ ID NO: 41)	CCTTTGCCCAAGTTG (SEQ ID NO: 42)
Gelsolin	X04412	TGGACGTTTTTGATCGA AGAG (SEQ ID NO: 43)	AAGTCAAGGCTTCTGTCT TTTCTTCT (SEQ ID NO: 44)	CTTGAGAAATCCTTTC CAACC (SEQ ID NO: 45)

Table 14.

Gel No. 1	VEGF + DMSO - 48hr
Gel No. 2	Compound 1 + VEGF + DMSO - 48hr
Gel No. 3	VEGF + DMSO - 48hr

Table 15.

Spot #1202	Run #1	Run #2
Sample		
baseline	126	22.5
VEGF at 24h	437	192.4
VEGF at 48h	812	540
VEGF and compound 1 (1uM) at 24h	270	484.7
VEGF and compound 1 (1uM) at 48h	869	158

Table 16.

<u>SSP</u>	<u>Well</u>	<u>MALDI Mass Mapping result</u>	<u>MS-Fit MOWSE Score</u>	<u>Sequence Coverage</u>
1202	A6	Interstitial Collagenase Precursor	3.64E+07	31%

Table 17.

SSP	Well	Confirmed Peptide	File Name	MS/MS result	MASCOT Score
1202	A6	DIYSSFGFPR (SEQ ID NO: 46)	spotA6-1188.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	34
1202	A6	DGFFYFFHGTR (SEQ ID NO: 47)	spotA6prod1393-2.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	22

Table 18.

HUVEC SAMPLE ¹	Average pro-MMP1 (ng/ml)	Standard Deviation
VEGF 10 min	4.66	0.3079
DMSO 10 min	4.64	0.1003
compound 1 @ 10 nM 10 min	5.41	0.1224
Compound 1 @ 100 nM 10 min	5.78	0.3158
Compound 1 @ 1 uM 10 min	5.04	0.331
VEGF 8 hr	16.47	1.0048
DMSO 8 hr	17.63	1.2563
Compound 1 @ 10 nM 8 hr	14.93	1.1245
Compound 1 @ 100 nM 8 hr	12.75	0.6686
Compound 1 @ 1 uM 8 hr	14.48	1.0551
VEGF 24 hr	45.71	3.06
DMSO 24 hr	79.94	4.50
Compound 1 @ 10 nM 24 hr	70.21	4.82
Compound 1 @ 100 nM 24 hr	50.26	1.24
Compound 1 @ 1 uM 24 hr	50.42	2.42
VEGF 48 hr	244.74	3.91
DMSO 48 hr	234.72	10.85
Compound 1 @ 10 nM 48 hr	135.35	1.04
Compound 1 @ 100 nM 48 hr	128.75	11.05
Compound 1 @ 1 uM 48 hr	103.09	3.60

¹Time points indicated (10 min, 8h, 24h, 48h) refer to the period of time post-VEGF treatment after which samples were isolated.

Table 19.

	Pro-MMP1 (ng/ml)	FC vs d1 Pre ¹	% Change vs d1 Pre
Pt 3 d1 Pre ²	0.3115		
d1 24 hr	0.2837	-1.097990835	-8.924558587
d13 Pre	0.6756	2.168860353	116.8860353
d13 12 hr	0.6235	2.001605136	100.1605136
d13 24 hr	0.4035	1.295345104	29.53451043
Pt 4 d1 Pre	0.5214		
d1 24 hr	0.8938	2.869341894	71.42309168
d13 Pre	0.6246	2.005136437	19.79286536
d13 12 hr	0.4579	1.469983949	-12.17874952
d13 24 hr	0.4514	1.449117175	-13.42539317
Pt 5 d1 Pre	0.5739		
d1 24 hr	0.323	1.036918138	-43.71841784
d13 Pre	0.7269	2.333547352	26.65969681
d13 12 hr	0.6874	2.206741573	19.77696463
d13 24 hr	0.4171	1.339004815	-27.32183307
Pt 6 d1 Pre	0.2969		
d1 24 hr	0.6818	2.188764045	129.6396093
d13 Pre	0.7597	2.438844302	155.8773998
d13 12 hr	0.7992	2.56565008	169.1815426
d13 24 hr	1.066	3.422150883	259.043449
Pt 7 d1 Pre	0.5743		
d1 24 hr	0.7334	2.354414125	27.70329096
d13 Pre	0.7374	2.367255217	28.39979105
d13 12 hr	0.5154	1.654574639	-10.25596378
d13 24 hr	0.7203	2.312359551	25.42225318
Pt 8 d1 Pre	0.2879		
d1 24 hr	0.3664	1.176243981	27.26641195
d13 Pre	1.7166	5.510754414	496.2486975
d13 12 hr	1.1071	3.554093098	284.5432442
d13 24 hr	0.8494	2.726805778	195.0329976
Pt 9 d1 Pre	0.7786		
d1 24 hr	0.4816	1.546067416	-38.14538916
d13 Pre	0.4931	1.582985554	-36.66837914
d13 12 hr	1.047	3.361155698	34.47212946
d13 24 hr	2.6022	8.353772071	234.2152582
Pt 10 d1 Pre	0.3613		
d1 24 hr	0.2396	-1.300083472	-33.68391918
d13 Pre	1.2937	4.153130016	258.0680875
d13 12 hr	1.4224	4.566292135	293.6894547
d13 24 hr	1.0684	3.429855538	195.7099363

Table 19 cont.

Pt 11 d1 Pre	0.299		
d1 24 hr	0.2866	-1.08688067	-4.147157191
d13 Pre	0.6931	2.225040128	131.8060201
d13 12 hr	0.4496	1.443338684	50.36789298
d13 24 hr	1.1685	3.751203852	290.8026756
Pt 12 d1 Pre	0.8587		
d1 24 hr	0.5418	1.739325843	-36.90462327
d13 Pre	2.1689	6.962760835	152.5794806
d13 12 hr	2.1494	6.900160514	150.308606
d13 24 hr	5.9226	19.01316212	589.7170141

¹ Fold change of pro-MMP1 levels are indicated by "FC vs d1 pre". These levels were calculated by dividing the levels of pro-MMP1 after drug treatment by the MMP1 levels present before drug treatment (d1 pre).

² Patient number is indicated (Pt), time point of sampling is indicated pre-treatment (d1 pre), 24 hours post first treatment (d1 24h), after 13 days of treatment (d13 pre), after 13 days and 12 hours post-treatment (d13 12h), and 13 days and 24hours of treatment (d13 24h).

Table 20.

5000 ng/mL Bio-migG	4000 ng/mL Bio-migG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1 α	IL-1 β	IL-1 α R1	0 ng/mL Bio-migG	3000 ng/mL Bio-migG	2000 ng/mL Bio-migG
5000 ng/mL Bio-migG	4000 ng/mL Bio-migG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1 α	IL-1 β	IL-1 α R1	0 ng/mL Bio-migG	3000 ng/mL Bio-migG	2000 ng/mL Bio-migG
5000 ng/mL Bio-migG	4000 ng/mL Bio-migG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1 α	IL-1 β	IL-1 α R1	0 ng/mL Bio-migG	3000 ng/mL Bio-migG	2000 ng/mL Bio-migG
5000 ng/mL Bio-migG	4000 ng/mL Bio-migG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1 α	IL-1 β	IL-1 α R1	0 ng/mL Bio-migG	3000 ng/mL Bio-migG	2000 ng/mL Bio-migG
1000 ng/mL Bio-migG	800 ng/mL Bio-migG	600 ng/mL Bio-migG	400 ng/mL Bio-migG	300 ng/mL Bio-migG	200 ng/mL Bio-migG	100 ng/mL Bio-migG	80 ng/mL Bio-migG	60 ng/mL Bio-migG	50 ng/mL Bio-migG	40 ng/mL Bio-migG	30 ng/mL Bio-migG	20 ng/mL Bio-migG	10 ng/mL Bio-migG	5 ng/mL Bio-migG	Blank
1000 ng/mL Bio-migG	800 ng/mL Bio-migG	600 ng/mL Bio-migG	400 ng/mL Bio-migG	300 ng/mL Bio-migG	200 ng/mL Bio-migG	100 ng/mL Bio-migG	80 ng/mL Bio-migG	60 ng/mL Bio-migG	50 ng/mL Bio-migG	40 ng/mL Bio-migG	30 ng/mL Bio-migG	20 ng/mL Bio-migG	10 ng/mL Bio-migG	5 ng/mL Bio-migG	Blank
1000 ng/mL Bio-migG	800 ng/mL Bio-migG	600 ng/mL Bio-migG	400 ng/mL Bio-migG	300 ng/mL Bio-migG	200 ng/mL Bio-migG	100 ng/mL Bio-migG	80 ng/mL Bio-migG	60 ng/mL Bio-migG	50 ng/mL Bio-migG	40 ng/mL Bio-migG	30 ng/mL Bio-migG	20 ng/mL Bio-migG	10 ng/mL Bio-migG	5 ng/mL Bio-migG	Blank
1000 ng/mL Bio-migG	800 ng/mL Bio-migG	600 ng/mL Bio-migG	400 ng/mL Bio-migG	300 ng/mL Bio-migG	200 ng/mL Bio-migG	100 ng/mL Bio-migG	80 ng/mL Bio-migG	60 ng/mL Bio-migG	50 ng/mL Bio-migG	40 ng/mL Bio-migG	30 ng/mL Bio-migG	20 ng/mL Bio-migG	10 ng/mL Bio-migG	5 ng/mL Bio-migG	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1 α	sgp130	TARC	TGF- β 1	TNF- α	TNF- β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1 α	sgp130	TARC	TGF- β 1	TNF- α	TNF- β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1 α	sgp130	TARC	TGF- β 1	TNF- α	TNF- β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1 α	sgp130	TARC	TGF- β 1	TNF- α	TNF- β	TNF-R1	TNF-RII	VEGF	Blank
Blank	IL-2	IL-6 α R	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1 β	MIP-1 α	NAP-2
Blank	IL-2	IL-6 α R	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1 β	MIP-1 α	NAP-2
Blank	IL-2	IL-6 α R	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1 β	MIP-1 α	NAP-2
Blank	IL-2	IL-6 α R	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1 β	MIP-1 α	NAP-2

Table 21.

Patient	1, 2, 3	Patient	1, 2, 3
• ENA-78	(-) ↓ ↓	TNFR1	↑ ↑ (-)
• MPIF-1	(-) (-) ↓	VEGF	↑ ↑ (-)
• GCP-2	↑ (-) (-)	Flt3L	↑ ↑ ↑
• Amphireg	↑ (-) (-)	PLGF	↑ ↑ (-)
• IL-1 α	↑ ↑ (-)	IL6	↑ ↑ (-)
• IL-1 β	↑ ↑ (-)	MCP-1	↑ ↑ (-)
• IL-2	↑ ↑ (-)	TNF α	↑ ↑ (-)
• MIG	(-) ↓ (-)	TARC	↑ (-) (-)
• NT4	↑ (-) ↑	MMP7	↑ ↑ ↓
• GCP-2	↑ ↑ (-)	MMP9	(-) (-) ↑
• IGFBP-1	↑ ↑ ↑	leptin	(-) ↑ (-)
• GRO- β	↑ (-) ↑		

Table 22.

	Patient 1		Patient 2		Patient 3	
	ELISA	Ab Chip	ELISA	Ab Chip	ELISA	Ab Chip
VEGF	32	2.7	72	4.3	3	1.8
PLGF	13	4.6	25.1	21.7	5.3	1.6
IL-6	29	2.9	11.6	3.7	0.9	0.99
IL-8	2	1.5	2.7	1.8	0.77	1.7
FLT3 L	10.3	13.9	6.7	7.7	2.6	6.2
MCP-1	2.2	2.5	1.93	2	1.0	1.4

We claim:

1. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

2. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

3. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and
 (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),
 wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

4. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising

(a) exposing the mammal to the test compound; and
 (b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-

cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

5. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-

binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

6. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo

sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

7. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb

gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

8. A method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic

transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in the same type of mammal without cancer, the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

9. The method of any one of claims 1-8, wherein the mammal is a human, rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate or monkey.

10. The method of any one of claims 1-8, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one mammalian biological tissue from the mammal.

11. The method of claim 10, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

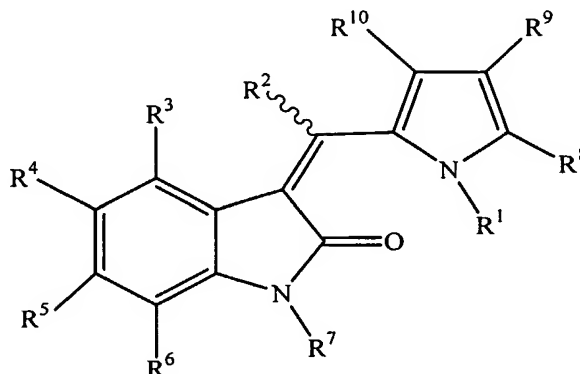
12. The method of claim 10, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

13. The method of any one of claims 1-8, wherein the mammal has cancer.

14. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is an indolinone compound.

15. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is:

a pyrrole substituted 2-indolinone having the formula:



wherein:

R^1 , R^2 and R^7 are hydrogen;

R^3 , R^4 , R^5 , and R^6 are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

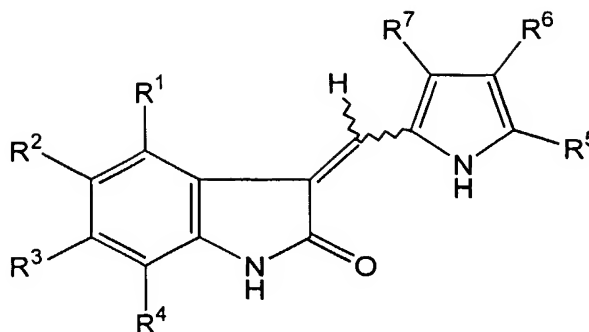
R^8 is unsubstituted lower alkyl;

R^9 is $-(CH_2)(CH_2)C(=O)OH$; and

R^{10} is unsubstituted lower alkyl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_nR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5 , R^6 or R^7 must be $-C(O)R^{10}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl and aryl;

R^{10} is selected from the group consisting of hydroxy, alkoxy, aryloxy, $-N(R^{11})(CH_2)_nR^{12}$, and $-NR^{13}R^{14}$;

R^{11} is selected from the group consisting of hydrogen and alkyl;

R^{12} is selected from the group consisting of $-NR^{13}R^{14}$, hydroxy, $-C(O)R^{15}$, aryl, heteroaryl, $-N^+(O^-)R^{13}R^{14}$, $-N(OH)R^{13}$, and $-NHC(O)R^a$ (wherein R^a is unsubstituted alkyl, haloalkyl, or aralkyl);

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^{13} and R^{14} may combine to form a heterocyclo group;

R^{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R^{16} is selected from the group consisting of hydroxy, $-C(O)R^{15}$, $-NR^{13}R^{14}$ and $-C(O)NR^{13}R^{14}$;

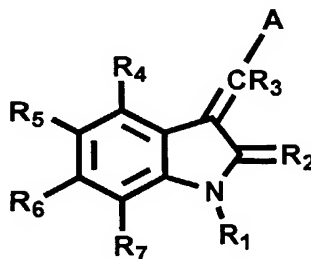
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R^{20} is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R_1 is H;

R_2 is O or S;

R_3 is hydrogen;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-

oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R or CONRR';

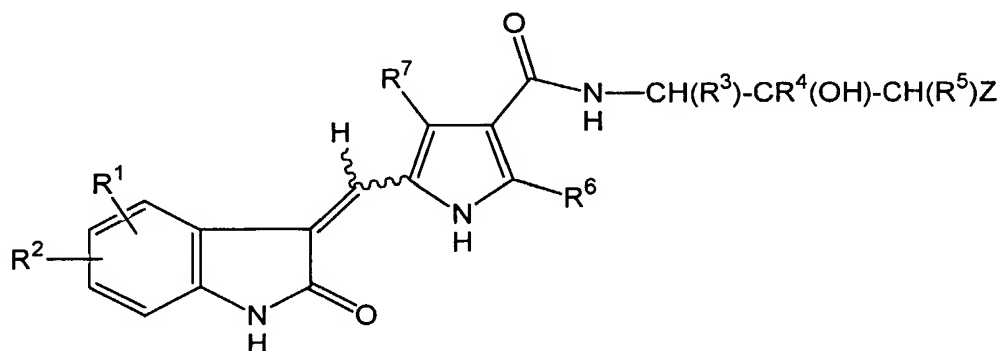
n is 0-3;

R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R¹ is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, -C(O)R⁸, -NR⁹R¹⁰ and -C(O)NR¹²R¹³;

R² is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, -NR⁹R¹⁰, -NR⁹C(O)R¹⁰, -C(O)R⁸, -S(O)₂NR⁹R¹⁰ and -SO₂R¹⁴ (wherein R¹⁴ is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R³, R⁴ and R⁵ are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or -NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are independently hydrogen or alkyl; or R¹⁵ and R¹⁶ together with the nitrogen atom to which they are attached from a heterocycloamino group;

R⁶ is selected from the group consisting of hydrogen or alkyl;

R⁷ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and -C(O)R¹⁷ as defined below;

R⁸ is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

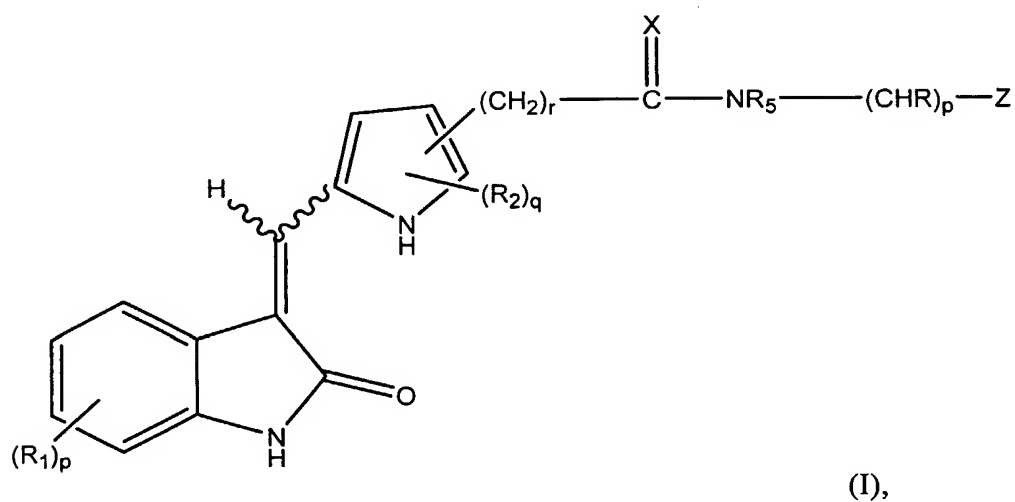
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound A) or a pharmaceutically acceptable salt thereof.

17. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one (Compound B) or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula I:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$, $-NR_9R_{10}$, $-NR_9C(O)-R_{12}$ and $-C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, $-C(O)-R_8$, and SO_2R'' , where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_3 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$ and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

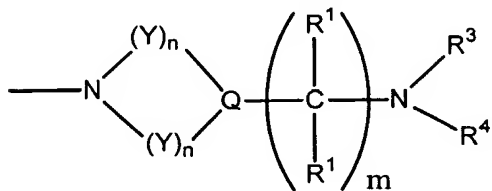
R_8 is selected from the group consisting of $-OH$, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of $-OH$, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

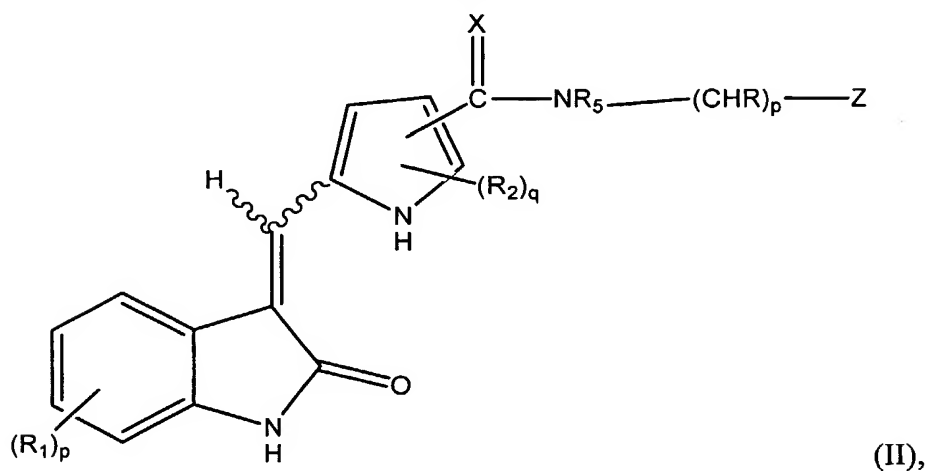
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

19. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula II:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$, $-NR_9R_{10}$, $-NR_9C(O)-R_{12}$ and $-C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, $-C(O)-R_8$, and SO_2R'' , where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, $-C(O)-R_8$ and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

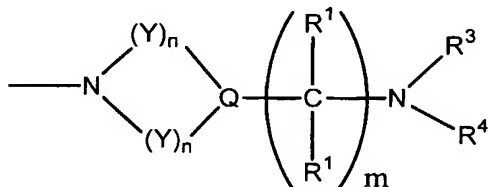
R_8 is selected from the group consisting of $-OH$, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of $-OH$, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

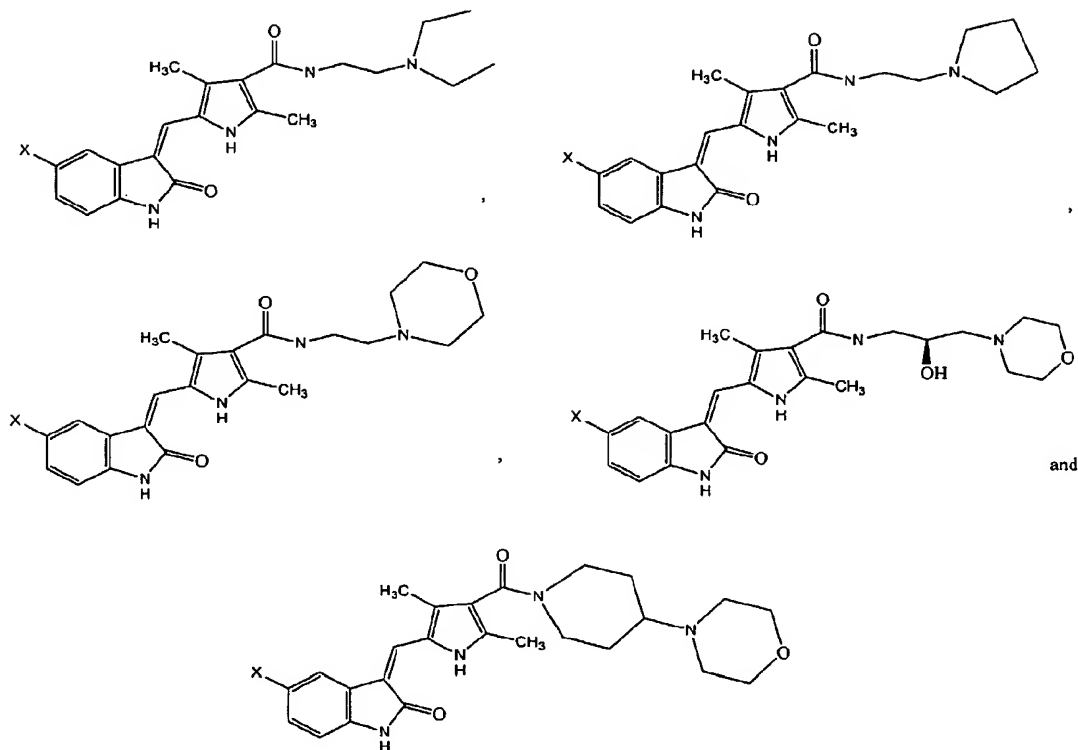
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 18, wherein the compound that inhibits tyrosine kinase activity is selected from the group consisting of:



wherein X is F, Cl, I or Br;

or a pharmaceutically acceptable salt thereof.

21. The method of claim 18, wherein the compound of Formula I is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1).

22. A kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein

A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

23. A kit of claim 22, wherein said instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal

phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

24. A method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

25. The method of claim 24, wherein the tyrosine kinase inhibitor is a compound of Formula I or salt thereof.

26. The method of claim 25, wherein the compound of Formula I or salt thereof is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1) or salt thereof.

27. A method of claim 24, wherein the adverse event is debilitating fatigue.

28. The method of claim 24, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one biological tissue from the mammal.

29. The method of claim 24, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

30. The method of claim 24, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

Figure 2.

				DIFFERENCE VALUES (percent change)									
				pt 1 pre v 4 hr post d.1 200 mg/m2	pt 8 pre v 4 hr post d.1 200 mg/m2	pt 9 pre v 4 hr post d.1 200 mg/m2	pt 10 pre v 4 hr post d.1 200 mg/m2	pt 12 pre v 4 hr post d.1 200 mg/m2	pt 1 d1 pre vs 4 hr post 800 vs 200 mg/m2	pt 1 pre-dose d 28vs d1 pre-dose 200 mg/m2			
Cmax (ug/ml) AUC ₀₋₂₄ (ug hr/ml) Exposure>2.3 ug/ml (hrs)				16.4	2.5	7.4	15.8	15.1	27	8.9			
				94.7	36.2	50.2	148.4	102.4	175.3	57.2			
				13.2	2.2	6.6	19.8	12.5	20.6	9.7			
CLASS	spot#	pl	MW	104				79	16	46	204	0	
	1	5	5.79	140776									

Difference= (1- spot% sample X/ spot% sample ref)/(-100)

Duplicate gels were run for each (pre and post) sample. Averaged values were used for the calculations.

- is up in post versus pre
- + is down in post versus pre

IEF with pH 4-8 ampholines. Fifty ng of IEF standard tropomyosin added to each sample before loading.

SDS slb gels are 10%

Figure 3.

SPOT #	w/SU006668	MS-MS Identification	potential role
5	↓	ITIH4 (inter-alpha globulin inhibitor H4)	acute phase IL6 induced

Figure 4A.

	Patient #	017	019	022	027	028
Gene Name	Accession #	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.
VEGF	AF022375	3.51/ND	1.49/0.8	1.68/ND	2.91/0.5	0.27/0.198
MAPK Kinase3	L36719	1.14/0.65	0.26/2.56	0.75/0.67	0.54/1.96	0.21/0.39
PECAM	L34657	0.72/ND	0.99/0.60	1.01/ND	0.75/0.92	0.22/0.23
Hemoglobin Epsilon 1	A1349593	ND/1.53	ND/3.05	ND/ND	ND/3.06	ND/2.9
Vinculin	M33308	32.19/1.96	1.43/0.75	1.71/1.21	1.84/0.62	8.24/3.72

¹Normalized against 18S

F.C. = Fold Change

ND = Not detected

Table 4B.

Patient #	Taqman/Affy Fold Change	SU6668 Dose (mg/m ²)	SU6668 Cmax (µg/ml)	SU6668 AUC (µg*hr/ml)	SU6668 Exposure >2.3 µg/ml (hrs)	Tumor Types
17	32.19/1.96	200 BID	11.5	66.1	11	Colon/Rectal
27	1.84/0.62	400 BID	10.3	71.2	9.1	Colon/Rectal
28	8.24/3.72	400 BID	13	164.3	21.3	Prostate

Figure 6.

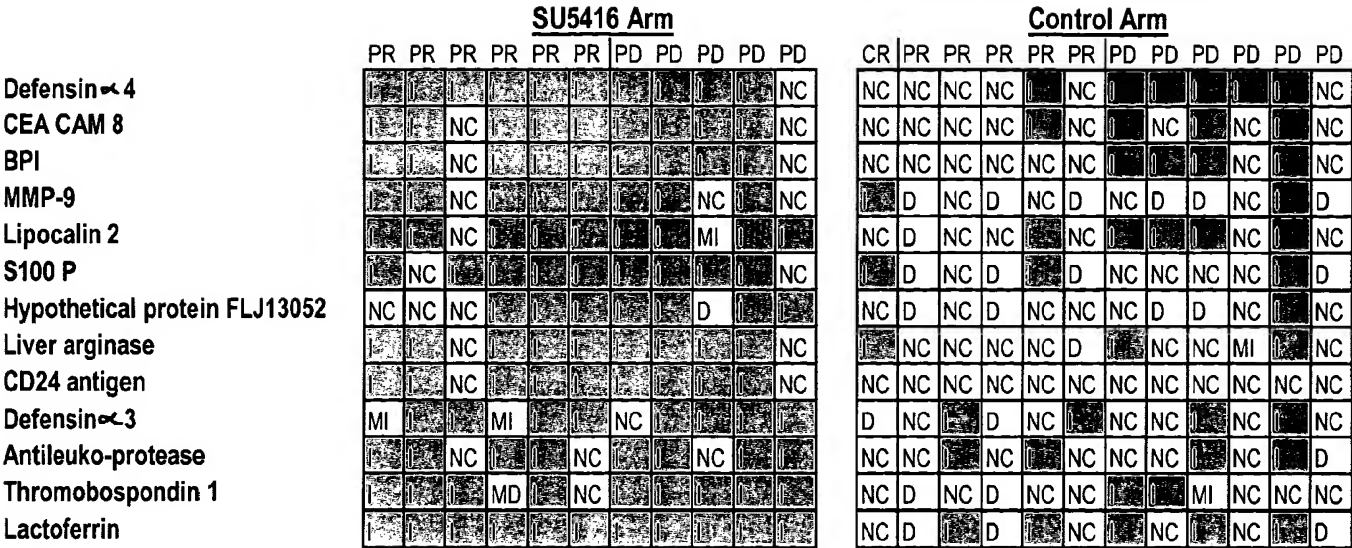


Figure 7.

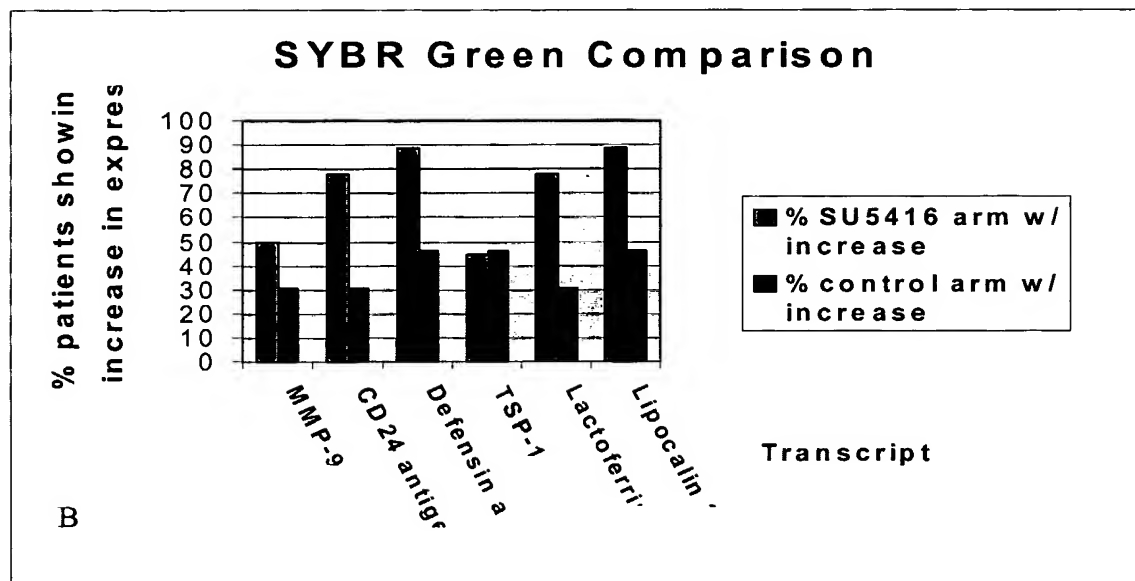
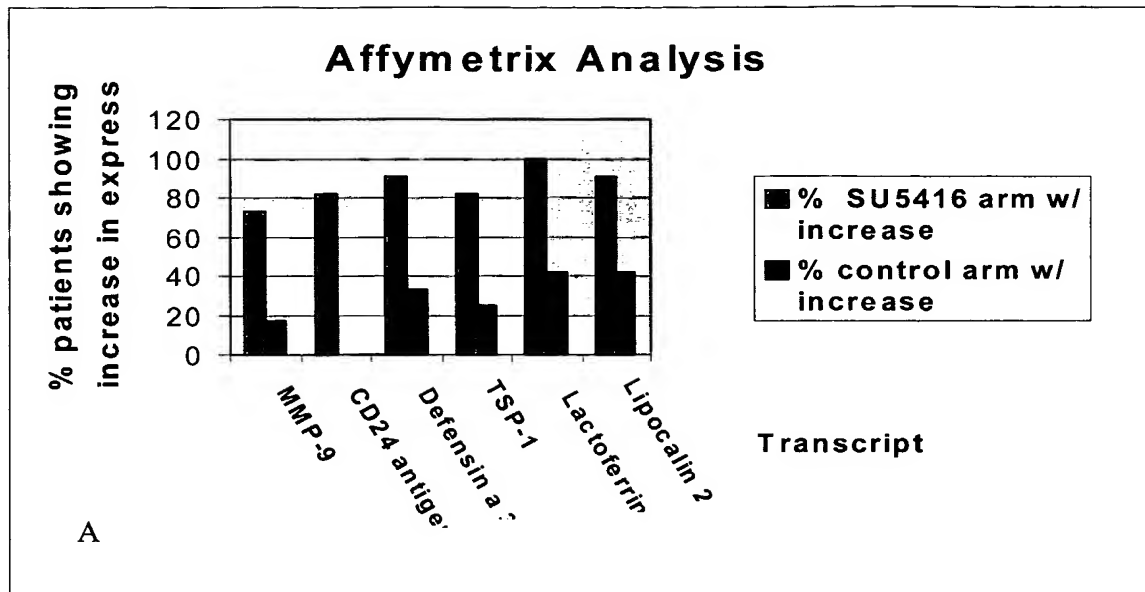


Figure 8.

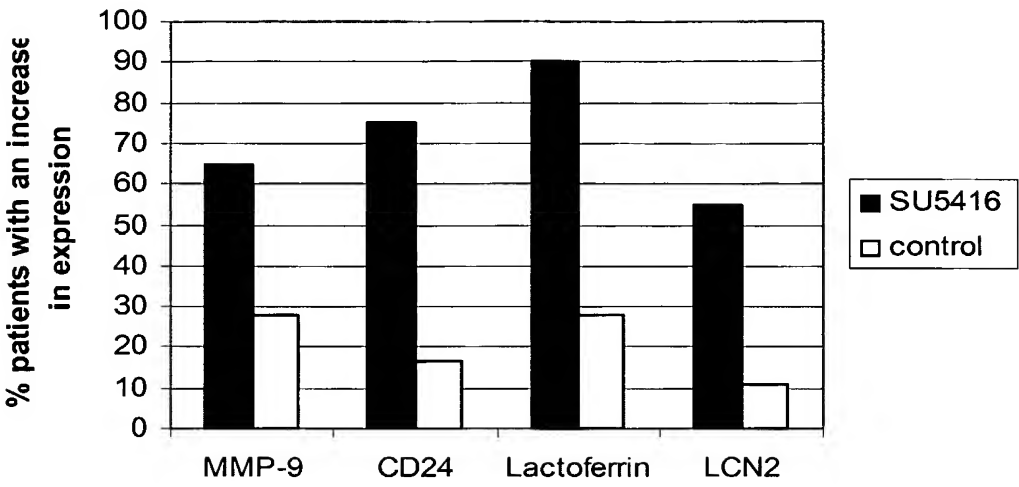


Figure 9.

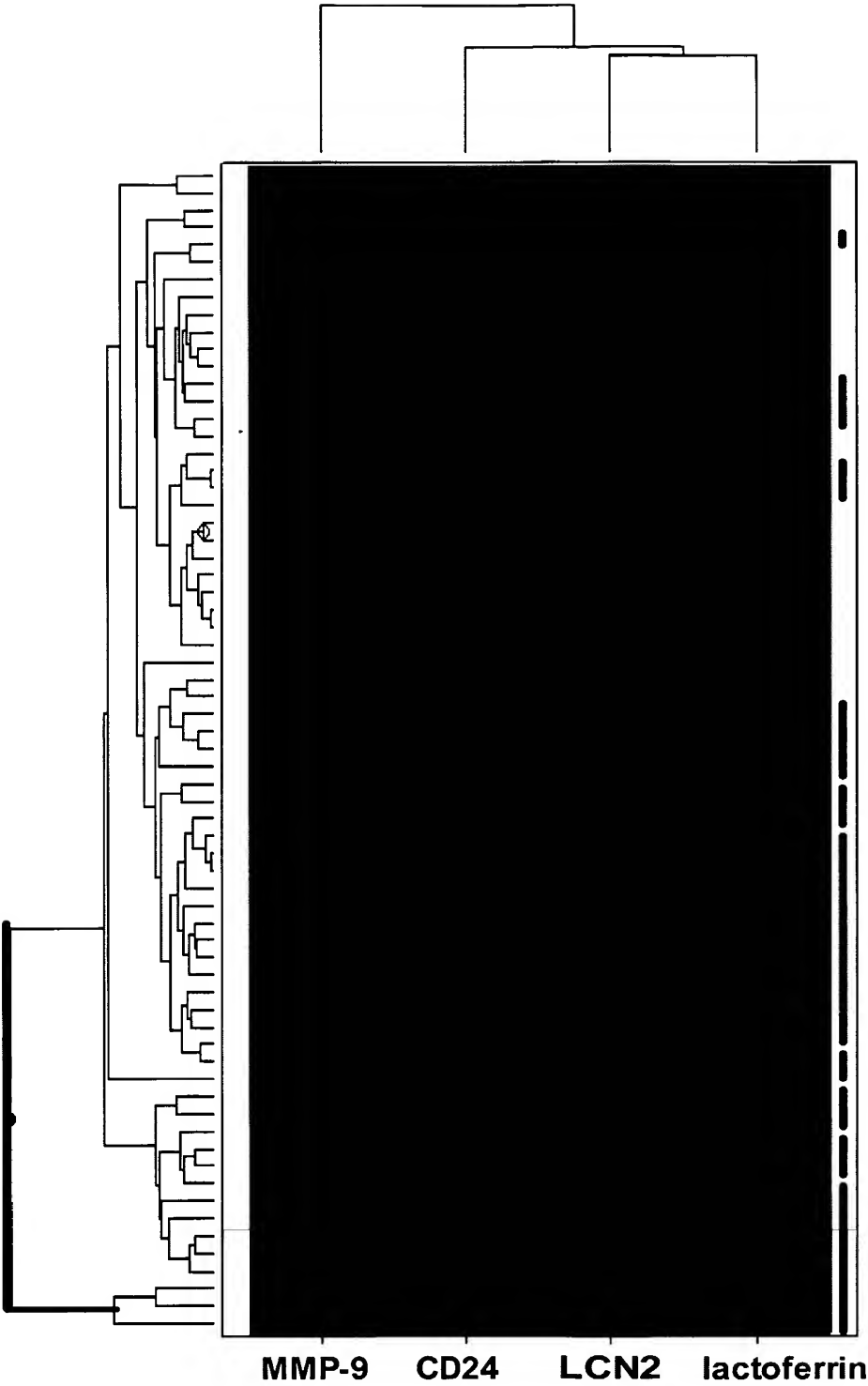
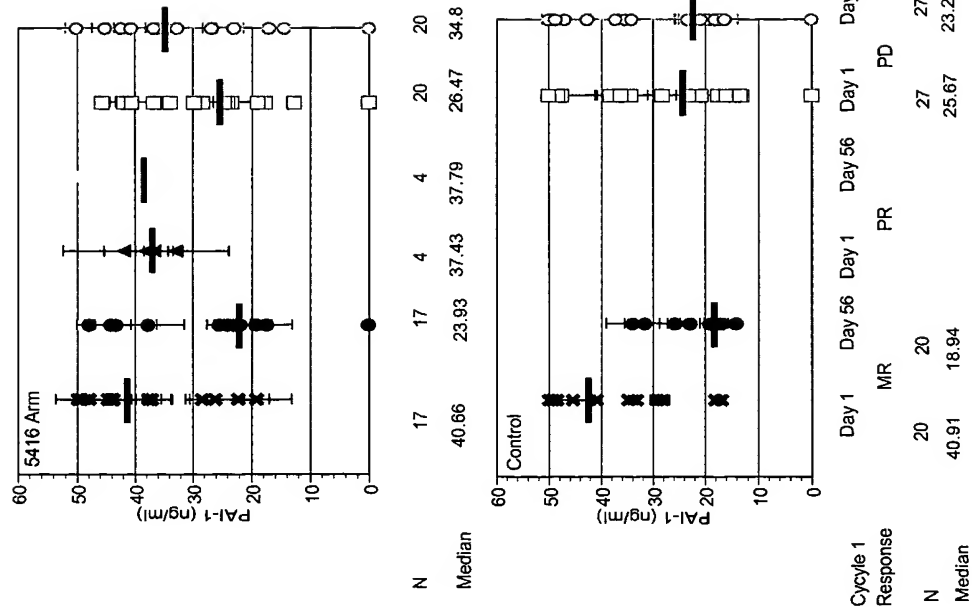


Figure 10.



Median levels of PAL-1 are indicated by a solid bar.
MR = minor response (cycle 1), PR = partial response (cycle 1), PD = progressive disease (cycle 1).

Figure 11.**mRNA and protein sequences for human lactoferrin****X53961****Human mRNA for lactoferrin [gi:34415]**

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1 gactcctagg ggcttcgaga cctagtggga gagaagaac atcgagcag ccaggcagaa
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Protein sequence of human lactoferrin

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LGPQYVAGITNLKKCSTSPLEACEFLRK

mRNA and protein sequences for human lipocalin-2 (LCN2)

NM_005564

Homo sapiens lipocalin 2 (oncogene 24p3) (LCN2), mRNA [gi:5031852]

```
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181 atttcagag aagacaaaga ccgcaaaag atgtatgcca ccatctatga gctgaaagaa
241 gacaagagct acaatgtcac ctccgtctg ttaggaaaa agaagtgtga ctactggatc
301 aggacttttg ttccaggttg ccagcccggc gaggcacgc tgggcaacat taagagttac
361 cctggattaa cgattacct cgtccgagt gtgagcacca actacaacca gcatgctatg
421 gtgttcttca agaaagtct taaaacagg gagtactca agatcacct ctacgggaga
481 accaaggagc tgacttcgga actaaaggag aacttcacc gcttctcaa atatctgggc
541 ctccctgaaa accacatgt ctccctgtc ccaatcgacc agtgatcga cggtcga
```

Note: there is an additional 3' exon, not represented in the mRNA sequence above, that is included in the sequence that Affymetrix used in designing probes for LCN2 expression (and which was used in designing RT-PCR primers). The additional sequence is as follows:

```
1 ggtgccgcca gtcgccgac cagccgaac accattgagg gagctgggag accctcccca
61 cagtgccacc catgcagctg ctcccaggc caccgcgtg atggagcccc acctgtctg
121 ctaataaac atgtgc
```

Protein sequence for human lipocalin-1 (LCN2)

```
MPLGLLWLGLALLGALHAQAQDSTSDLIPAPLSKVPLQQNFQD
NQFQ GKWYVVG LAGNAILREDKDPQKMYATIYELKEDKSYNVTSVLFRKKKCDYWIRT
FVPGCQPGFTLGNIKSYPLTSYLVRVSTNYNQHAMVFFKKVSQNREYFKITLYGR
TKELTSELKENFIRFSKYLGLPENHIVFPVPIDQCIDG
```

mRNA and protein sequences for human MMP-9

NM_004994 Homo sapiens matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase) (MMP9), mRNA [gi:482835]

```

1 agacacctct gccctcacca tgagcctctg gcagcccctg gtcctggtgc tctggtgct
61 gggctgtgctc ttgctgccc ccagacagcg ccagtccacc ctgtgtctct tcctggaga
121 cctgagaacc aatctcaccg acaggcagct gcagaggaa tacctgtacc gctatggtta
181 cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct
241 ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat
301 gcgaacccca cggtcgggg tcccagacct gggcagattc caaacctttg agggcgacct
361 caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg
421 ggcggtgatt gacgacgct ttgcccgcg cttcgactg tgagcgcg tgacccgct
481 caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagttg gtgtcgcgga
541 gcacggagac gggtatccct tcgacgggaa ggacgggctc ctggcacacg ccttctctc
601 tggccccggc attcaggag acgcccattt cgacgatgac gaggttggt cctgggcaa
661 gggcgctgtg gtccaactc ggtttgaaa cgagatggc gcggcctgcc acttcccctt
721 catctcgag ggcgctctc actctgctg caccaccgac ggtcgctccg acggcttgcc
781 ctggtgcagt accacggcca actacgacac cgacgaccgg ttggcttct gccccagca
841 gagactctac acccgggacg gcaatgctga tgggaaacc tggcagttc cattcatctt
901 ccaaggccaa tctactccg cctgcaccac ggacggtcgc tccagggct accgctggtg
961 cgccaccacc gccaactacg accgggacaa gctcttcggc ttctgccga cccgagctga
1021 ctgacgggtg atggggggca actcggcggg ggagctgtgc gtcttccct tcaatttct
1081 gggtaaggag tactcgacct gtaccagcga gggccgcgga gatgggcgcc tctggtgcgc
1141 taccacctcg aacttgaca gcgacaagaa gtggggcttc tgcccgacc aagdatacag
1201 ttgttctc gtggcggcg atgagtcgg ccacgcgctg ggcttagatc attctcagt
1261 gccggaggcg ctcattgacc ctatgtacc cttactgag gggcccccct tgcataagga
1321 cgacgtgaat ggcacccggc accttatgg tctcgccct gaacctgagc cagggcttcc
1381 aaccaccacc acaccgcagc ccacggctcc cccgacggtc tgccccaccg gacccccac
1441 tgtccacccc tcagagcgcc ccacagctgg cccacaggt cccccctcag ctggccccac
1501 aggtccccc actgtggcc cttctacggc cactactgtg ctttgagtc cgggtggacga
1561 tgcctgcaac gtgaacatct tcgacgcat cgcggagatt gggaaccagc tgtatttgtt
1621 caaggatggg aagtactggc gattctctga gggcaggggg agccggccgc agggcccctt
1681 ccttatgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggct ttgaggagcc
1741 gctctccaag aagcttttct tcttcttg gcgccaggtg tgggtgtaca caggcgctc
1801 ggtgctgggc ccgaggcgtc tggacaagct gggcctggga gccgacgtg cccaggtgac
1861 cggggccctc cgagtgga gggggaagat gctgctgttc agcggcgcc gcctctggag
1921 gttcgacgtg aaggcgca tgggtgatcc ccggagcgcc agcgaggtg accggtgtt
1981 cccgggggtg ctttggaca cgcacgacgt cttcagtag cgagagaaag cctatttctg
2041 ccaggaccgc ttctactggc gcttgagttc ccgagtgag tgaaccagg tggaccaagt
2101 gggctacgtg acctatgaca tctgcagtg ccctgaggac tagggctccc gtctgcttt
2161 gcagtccat gtaaatccc actgggacca accctgggga aggagccagt ttgccggata
2221 caaactggta ttctgttctg gaggaaggg aggagtgag gtgggctggg ccctctctt
2281 tcaccttgt ttttgttg agtgttcta ataaacttg attcttaac cttt

```

Protein sequence for Homo sapien MMP9

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLFPGDLRTNLTDRQL
AEEYLYRYGYTRVAEMRGESKSLGPALLLLQQLSLPETGELDSATLKAMRTPRCGVP
DLGRFQTFEGDLKWHHHNITYWIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVY
SRDADIVIQFGVAEHGDGYFPDGDGLLAHAFPPGPGIQGDAHFDDELWSLGKGVVV
PTRFGNADGAACHFPFIFEGRSYSACTTDGRSDGLPWCSTTANYDTDDRFGFCPSERL
YTRDGNADGKPCQFPFIFQGQSYSACTTDGRSDGYRWCATTANYDRDKLFGFCPTRAD
STVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGRLWCATTSNFDSDKKWGFCPDQG
YSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPPLHKDDVNGIRHLYGPRPEPE
PRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGPPTAGPSTATTVP
LSPVDDACNVNIFDAIAEIGNQLYLFKDGKYWRFSEGRGSRPQGPFLIADKWPALPRK
LDSVFEEPLSKKLFFFSGRQVWVYTASVLGPRRLDKLGLGADVAQVTGALRSGRGKM
LLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYWRV
SSRSELNQVDQVG YV TYDILQCPED

mRNA and protein sequences for human CD24**L33930 Homo sapiens CD24 signal transducer mRNA, complete cds and 3' region [gi:500848]**

1 cggttctcca agcaccacgc atcctgctag acgcgccgcg caccgacgga ggggacatgg
61 gcagagcaat ggtggccagg ctggggctgg ggctgctgct gctggcactg ctctaccca
121 cgcagattta ttccagtga acaacaactg gaacttcaag taactctcc cagagtactt
181 ccaactctgg gttggcccca aatccaacta atgccaccac caaggcggct ggtggtgccc
241 tgcagtcaac agccagtctc ttctgggtct cactctctct tctgcatctc tactcttaag
301 agactcagcg caagaaacgt cttctaaatt tcccactctt ctaaacccaa tccaaatggc
361 gtctggaagt ccaatgtggc aaggaaaaac aggtcttcat cgaatctact aattccacac
421 cttttattga cacagaaaat gtgagaatc ccaaatttga ttgatttga gaacatgtga
481 gaggtttgac tagatgatga atgccaatat taaatctgct ggagtttcat gtacaagatg
541 aaggagagcg aacatccaaa atagttaaga catgatttcc ttgaatgtgg cttgagaaat
601 atggacactt aatactacct tgaaaataag aatagaataa aaggatggga ttgtggaatg
661 gagattcagt ttctattgtt tcattaattc tataaggcca taaaacaggt aatataaaaa
721 gttccatcg atctatttat atgtacatga gaaggatcc ccagggtgta ctgtaattcc
781 tcaacgtatt gtttcgacgg cactaattta atgccgatat actctagatg aatgtttaca
841 ttgttgagct attgctgttc tcttggaac tgaactcact ttctctga ggctttggat
901 ttgacattgc atttgacctt ttaggtagta attgacatgt gccagggcaa tgaatgaatga
961 gaatctacc cagatccaag catcctgagc aactcttgat tatccatatt gagtcaaatg
1021 gtaggcattt cctatcacct gtttccattc aacaagagca ctacattctt ttagtctaac
1081 ggattccaaa gagtagaatt gcaatgacca cgaactaatt caaatgctt ttattatta
1141 ttatttttta gacagtctca cttgtcgcc caggccggag tgcagtgggt cgatctcaga
1201 tcagtgtacc atttgctcc cgggctcaag cgattctcct gcctcagcct cccaagtagc
1261 tgggattaca ggcacctgcc accatgcccg gctaattttt gtaattttag tagagacagg
1321 gtttcacat gttgccagg ctggtttaga actcctgacc tcaggtgatc caccgcctc
1381 ggctcccaa agtgctggga ttacaggctt gagccccgc gccagccat caaatgctt
1441 ttatttctg catatgtttg aatactttt acaatttaa aaaatgatct gttttgaagg
1501 caaaattgca aatctgaaa ttaagaaggc aaaatgtaa ggagtcaaac tataaatcaa
1561 gtatttggga agtgaagact ggaagctaatt ttgcataaat tcacaaactt ttactctt
1621 tctgtatata cattttttt ctttaaaaa caactatgga tcagaatagc aacatttga
1681 acactttttg ttatcagtca atatttttag atagttaga cctggctcta agcctaaaag
1741 tgggcttgat tctgcagtaa atcttttaca actgcctcga cacacataaa cttttttaa
1801 aatagacact ccccgaaatc tttgtttgt atggtcacac actgatgctt agatgttcca
1861 gtaatcta atatggccacag tagtcttgat gaccaaagtc cttttttcc atctttaga
1921 aactacatgg gaacaaacag atcgaacagt ttgaagcta ctgtgtgtgt gaatgaacac
1981 tcttgcttta ttccagaatg ctgtacatct attttgatt gtatatgtg gttgtgtatt
2041 tacgcttga ttcatagtaa cttcttatgg aattgatatt cattgaacga caaactgtaa
2101 ataaaaagaa acggtg

Protein sequences for human CD24

MGRAMVARLGLGLLLLALLPTQIYSSETTTGTSSNSSQSTSNS
GLAPNPTNATTKAAGGALQSTASLFVVSLSLHLYS

Figure 12. (Page 1 of 33)

D30655. Homo sapiens mRNA...[gi:485387]:

Eukaryotic initiation factor 4AII

DNA sequence:

```
1 gtggttttc ggatcatgtc tgggtggctcc gcggattata acagagaaca tggcggccca
61 gagggaaatg accccgatgg tgatcatcag agcaactgga atgagattgt tgataacttt
121 gatgatatga atttaaagga gtctctcctt cgtggcatct atgcttacgg ttgtgagaag
181 ccttccgcta ttcagcagag agctattatt cctgtatta aagggtatga tggattgct
241 caagctcagt caggactgg caagacagcc acatttgcta ttccatcct gcaacagttg
301 gagattgagt tcaaggagac ccaagcacta gtattggccc ccaccagaga actggctcaa
361 cagatccaaa aggtaatctt ggcacttga gactatatgg gagccactg tcatgcctgc
421 attggtgga aatggttcg aatgaaatg caaaaactgc aggtgaagc accacatatt
481 gttgttgga caccgggag agtgtttgat atgttaaaca gaagatacct ttctccaaa
541 tggatcaaaa tgtttgtt ggatgaagca gatgaaatgt tgagccgtgg tttaaggat
601 caaatctatg agattttcca aaaactaaac acaagtattc aggtgtgtt tgctctgcc
661 acaatgcaa ctgatgtgt ggaagtgacc aaaaaattca tgagagatcc aattgaatt
721 ctggtgaaa aggaagaatt gaccctgaa ggaatcaaac agttttatat taatgttga
781 agagaggaat ggaagtggg tacacttgt gactgtacg agacactgac cattacacag
841 gctgttatt ttctcaatac gaggcgaag gtggactggc tgactgagaa gatgatgcc
901 agagacttca cagtttctgc tctcatggt gacatggacc agaaggagag agatgttatc
961 atgagggaa tccggtcagg gtcaagtcgt gtctgatca ctactgactt gttggctgc
1021 gggattgatg tgacaacaagt gtctttggt ataaattatg atctacctac caatcgtgaa
1081 aactatattc acagaattgg cagagggggt cgatttgga ggaagggtg ggctataaac
1141 ttgttactg aagaagacaa gaggattctt cgtgacattg agactttcta caatactaca
1201 gtggaggaga tgcccatgaa tgggctgac cttatthaat tctgggatg agagttttg
1261 atcagtgct cgtgtgtct gaataggcga tcacaacgtg cattgtgctt cttctttg
1321 gaattttga atctgtctc aatgctcata acggatcaga aatacagatt ttgatagcaa
1381 agcgacgtta gtcgtgagct cttgtgagga aagtcattgg cttatcctc tttagagta
1441 gactgtggg gtgggtataa aagatgggg ctgtaaaatc ttcttctt agaaattat
1501 ttctagttc ttagaaaatg gttgtattg atgttctta tcatttaata atatactgt
1561 ggactaaaag atataagtc tgataaaat cagccaatta tgttaacta gcatactgc
1621 ctttattgtg ttgtcatta gcctgagtag aaaggcctt aaaattttt tagaaagcat
1681 tgaatgcat ttgtttgtt attgtattta tcaataaag tatttaatta gtgctaagt
1741 tgaactggac cctgttgcta agccccagca agcaatccta ggtagggtt aatccccagt
1801 aaaattgcca tattgcacat gtctaatga agtttgaatg taaataaat tgtatatca
1861 cttt
```

protein sequence:

```
MSGGSADYNREHGGPEGMDDPDGVIESNWNEIVDNFDDMNLKESLLRGIYAYGFEEKPSAIQQRAIIPC  
IKGYDVIAQAQSGTGKTATFAISILQQLEIEFKETQALVLAPTRELAQQIQKVILALGDYMGATCHACIGGTNVRNEMQKLQAEAPHIVVG  
TPGRVFDMLNRRYLSPKWIKMFVLDEADEMLSRGFKDQIYEIFQKLNTSIQVVFASATMPTDVLVETKKFMRDPIRILV  
KKEELTLEGIKQFYINVEREEWKDLTCLDYETLTITQAVIFLNTRRKVDWLTEKMHARDFTVSALHGDMDQKERVIM  
REFRSGSSRVLITDLLARGIDVQQVSLVINYDLPTNRENYIHRIGRGGFRGRKGVAINFVTEEDKRILRDIETFYNTTVE  
EMPMNVADLI
```

Figure 12. (Page 2 of 33)

M92383. Homo sapiens thym...[gi:339696]:

Homo sapiens thymosin beta-10 gene

DNA sequence:

```
1 cgtcctacat ctgcgcata cagccacg tgcgcacatc actgggggtg ccncgggaga
61 cagagccgct ggtagcctaa ggnngggggg cagccaggag aaagccccgc cgctgctgt
121 ccgcccctc gggtgccagc accgcccctg ctgcggcggg tgaggggcgg ggcggggccg
181 cggcgtatat aaggctaggc ggggcgccgc tctttgttt ctgctgcag caacgcgagt
241 gggagcacca ggaatcggg ctcggaacga gactgcacgg tgacgtgacg gccgggcggg
301 ggcccagggt gtggtcggat ccggtgcacc gcgggcgcgc aaccgggaca ggcgttctc
361 ggaccggacg cagggggccg gaccacgccc tgggaccgag aagaggggtg cggacgcgcc
421 cagatcctcg gcctggggc tgctcggcag cctggcgcg agtgccacgt cgagaggcgt
481 cggcggggag cgcggaagg gacggcctgc gccaggccc aggtcaagcg ccttggttg
541 ccactagga ttgtttaag aaaatggcag acaaaccaga catgggggaa atcgccagct
601 tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag
661 agagtgaagt tgcctcgtc tccgcgcccc agcccagccc ctaccctgc tctccttg
721 aaaccacac ctccacccc caccgcgcc ttgtcccg tggtggcgcc ccggcactc
781 ttacagttc acaaagcgc ttgttctc ccagcccaa gctcctct aaatccaca
841 cctcgtgtg ctatcacac cgggaagcac ctcggtgcg ggtgggggtg tgcagcnccc
901 ctccagcgc ccgtccgtc tcaagccatt gagcaggaga agcggagtga aattcctaa
961 gatcctggag gatttctac ccccgctc tcggagcacc ccagtcgctg atgtggagaa
1021 gagccacct gcaagatgga cagagtcga caagctgcac tgtgaacctg cgagcccg
1081 ccgatgccac cgccctgtg tcgtctgaag ggaccccc ccaatcgac tgccaaattc
1141 tcggtttgc ccggatatt atagaaaatt attgtatga ataataaaa taaaacacac
1201 ctggtggca tggctggcg tggctgagt gtttagtta gtaggggtc agtcactgc
1261 ag
```

protein sequence:

DCFKKMADKPDMEIASFDKAKLKTETQEKNTLPTKETIEQEKRSIS

Figure 12. (Page 3 of 33)

X79536. H.sapiens mRNA fo...[gi:496897]:

H.sapiens mRNA for hnRNPcore protein A1

DNA sequence:

```
1 ttaaagtctc tcttcacct gccgtcatgt ctaagtcaga gtctcctaaa gagcccgaac
61 agctgaggaa gctcttcatt ggagggttga gcttgaac aactgatgag agcctgagga
121 gccatttga gcaatgggga acgctcacgg actgtgtgt aatgagagat ccaaaccaca
181 agcgctctag gggctttggg ttgtcacat atgccactgt ggaggagggt gatgcagcta
241 tgaatgcaag gccacacaag gtggatggaa gattgttga accaaagaga gctgtctcca
301 gagaagattc tcaaagacca ggtgccact taactgtgaa aaagatatgt gtgtgtggca
361 ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg
421 aagtattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gccttataa
481 cctttgacga ccatgactcc gtggataaga ttgtcatca gaaataccat actgtgaatg
541 gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca
601 gccaaagagg tcgaagtgtt tctggaaact ttggtgtgtg tcgtggaggt ggttcggtg
661 ggaatgacaa ctccggtcgt ggaggaaact tcagtgtgtg tgggtgcttt ggtggcagcc
721 gtgtgtgtgt tggatatgtt ggcagtgggt atggctataa tggatttggc aatgatggaa
781 gcaattttgt aggtgtgtga agctacaatg attttgggaa ttacaacaat cagtctcaa
841 attttggacc catgaaggga ggaattttg gaggcagaag ctctggcccc tatggcgtgt
901 gaggccaata ctttcaaaaa ccacgaaacc aaggtggcta tggcggttcc agcagcagca
961 gtagctatgg cagtggcaga agattttaa tagggaggag tctgtacta gtcttatcag
1021 ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ccttgtgaag
1081 accttatct gagccactgt acttcgttat cagccatgc agttacatg agctgtctg
1141 cagctcgaaa ttccattttg tgaatgggtt ttttttta ataaactga ttaactt
```

protein sequence:

```
MSKSESPKEPEQLRKLFIGGLSFETTDESLRSHFEQWGTLTDCVVMRDPNTKRSRGFGFVYATVEEVDAAMNARP
HKVDGRVVEPKRAVSREDSQRPGAHLTVKKIFVGGIKEDTEEHHLRDYFEQYGKIEVIEIMTDRGSGKKRGFAFVTFD
DHDSVDKIVIQKYHTVNGHNCEVRKALSKQEMASASSSQRGRSGSNFGGGRGGGFGGNDNFGRGGNFSGRGGF
GGSRGGGGYGGSGDGYNGFGNDGSNFGGGGSYNDFGNYNQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKP
RNQGGYGGSSSSSYSGRRF
```

Figure 12. (Page 4 of 33)

X14046. Human mRNA for le...[gi:29793]:

Human mRNA for leukocyte antigen CD37

DNA sequence:

```
1 gctccccca ctgtcagcac ctctctgtg tggtagtg accgcttacc ccactaggtg
61 aagatgtcag cccaggagag ctgcctcagc ctcatcaagt acttcctctt cgttttcaac
121 ctctcttct tegtctcctg cagcctgac ttctgctcg gcatctggat cctcatcgac
181 aagaccagct tctgtcctt tgtgggctg gccttcgtgc ctctgcagat ctgttccaaa
241 gtctggcca tctcaggaat cttcaccatg ggcacgccc tctgggttg tgtgggggcc
301 ctaaggagc tccgtgcct cctgggctg tatttggga tctgctgct cctgtttgcc
361 acacagatca cctgggaat cctcatctcc actcagcggg cccagctgga gcgaagctg
421 cgggacgtcg tagagaaaac catccaaaag tacggcacca acccgagga gaccgggcc
481 gaggagagct gggactatgt gcagtccag ctgcgtgct gcggctggca ctaccgcag
541 gactggttcc aagtctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc
601 tctgtctaca actgtcggc gaccaacgac tccacaatcc tagataaggt gatctgccc
661 cagctcagca ggcttgaca cctggcgagg tccagacaca gtgcagacat ctgcgtgctc
721 cctgcagaga gccacatcia ccgcgagggc tgcgcgcagg gcctccagaa gtggctgcac
781 aacaacctta ttccatagt gggcatttgc ctgggcgtcg gcctactcga gctcgggttc
841 atgacgtct cgtattctct gtgcagaaac ctggaccacg tctacaaccg gctcgtcga
901 tacggttag ccccgccctc cccaaagtcc cgcggcgccc cgtcacgtg cgtcgggcac
961 ttccctgctg cctgtaaata ttgtttaat cccagttcg cctggagccc tccgccttca
1021 cattcccctg gggaccacg tggctgcgtg ccctgctgc tgcacctct cccacgggac
1081 ctggggcttt cgtccacagc ttctgtccc catctgtcgg cctac
```

protein sequence:

```
MSAQESCLSLIKYFLVFVNLFFFVLGSLIFCFGIWILIDKTSFVSFVGLAFVPLQIWSKVLAI SGIFTMGIALLGCVGALKEL
RCLLGLYFGMLLLLFATQITLGILISTQRAQLERSLRDVVEKTIQKYGTNPEETA AEESWDYVQFQLRCCGWHYPQDW
FQVLILRGN GSEAH RVP CSCYNLSATNDSTILDKVL PQLSRLGHLARSRHSADICAVPAESHIYREGCAQGLQKWLHN
NLISIVGICLG VGLLELGFMTLSIFLCRNLDHVYNRLARYR
```


Figure 12. (Page 5 of 33)

M32578. Human MHC class I...[gi:188305]:

Human MHC class II HLA-DR beta-1

DNA sequence:

```
1 agtttcctt gagtgagact tgctgtctt tctggccct ggtcctgtt tgttccag
61 catggtgtt ctgaagctt ctggagggtt ctacatggc gtgctgacg tgacactgat
121 ggtgctgagc tccccactg ctttggttg ggacacccg ccatgtttt tgcagcagga
181 taagtatgag tgcattttt tcaacgggac ggagcgggtg cggttcctg acagaggcat
241 ctataaccaa caggagaacg tgcgcttca cagcgacgtg ggggagtacc gggcggtagc
301 ggagctgggg cggcctgacg ctgagtactg gaacagccag aaggacatcc tggagcaggc
361 gcggggccgc gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt
421 gcagcggcga gttgagccta aggtgactgt gtatcctga aggacccaga cctgcagca
481 ccacaacctt ctggtctgct ctgtgaatg ttctatcca ggcagcattg aagtcagggtg
541 gttccggaac ggccaggaag agaaggctg ggtggtgtt acaggcctga ttcagaatgg
601 agactggacc ttccagattc tggtagtct ggaacagtt cctcggagt gagaggttta
661 cacctgcaa gtggagcacc caagcgtgac gagccctct acagtggaat ggagagcaca
721 gtctgaatct gcacagagca agatgctgag tggaatcgg ggctttgtc tgggcctgct
781 cttccttggg gccgggctat tcatctact caagaatcag aaagggcact ctggacttca
841 cccaacagga ctgtagact gaagtcaga tgaccacatt caagggggaa ccttctgcc
901 cagctttgca tgatgaaaag ctttctgct tggctttat tctccaca gagaggactt
961 tctcaggccc tggttgctc cggttcagc actctgcaga aaatgtccat ccttgtggct
1021 tctcagctc ctgcccttg cctgaagtcc cagcattgat ggcagtgcct catctcaac
1081 tttagtgct cctttacct aaccctacg cctccatgc atctgtact cccctgtgcc
1141 acaaatggac tacgttatta aattttctg aagcccagag ttaaaaatca tctgtccacc
1201 tggcaccaaa gacaaa
```

protein sequence:

```
MVCLKLPGGSYMAVLTVTLMVLSSPLALAGDTRPCFLQQDKYECHFFNGTERVRFHLHRGIYNQQENVRFDSDVGEY
RAVTELGRPDAEYWNSQKDILEQARA AVDTYCRHNYGAVESFTVQRRVEPKVTVYPARTQTLQHHNLLVCSVNGFY
PGSIEVRWFRNGQEEKAGVVSTGLIQNGDWTFQILVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRAQSESAQSKM
LSGIGGFVLGLLFLGAGLFIYFKNQKGHSGHLPTGLVS
```

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U54558. Homo sapiens tran...[gi:2351377]:

Homo sapiens translation initiation factor eIF3 p66 subunit mRNA

DNA sequence:

```
1 gaattcggca cgagctaacg cggccccgg caccgacccat ctgttgccat cccggccggc
61 cgaggccatt gcagattttg gaagatggca aagttcatga caccctgat ccaggacaac
121 ccctcaggct ggggtccctg tgcggttccc gagcagtttc gggatatgcc ctaccagccg
181 ttcagcaaag gagatcggct aggaaggtt gcagactgga caggagccac ataccaagat
241 aagaggtaga caataagta ctctctcag ttgtgtgtg gaagtaata tgcttattc
301 catgaggagg atgaaagtag ctccagctg gtggatacag cgcgcacaca gaagacggcc
361 taccagcggg atcgaatgag attgcccag aggaacctcc gcagagacaa agatcgtcgg
421 aacatgttgc agtcaacct gcagatcctg cctaagatg ccaaacagaa agagagagaa
481 cgcattcgac tgcagaaaaa gtccagaaa caattgggg ttaggcagaa atgggatcag
541 aaatcacaga aaccccgaga ctctcagtt gaagttcgtg gtgattggga agtgaaagag
601 gaaatggatt ttctcagtt gatgaagatg cgctacttgg aagtatcaga gccacaggac
661 attgagtgtt gtggggccct agaatactac gacaaagcct ttgaccgat caccacgagg
721 agtgagaagc cactgcggag catcaagcgc atctccaca ctgtcaccac cacagacgac
781 cctgtcatcc gcaagctggc aaaaactcag gggaatgtgt ttgccactga tgccatcctg
841 gccacgtga tgagctgtac ccgctcagtg tattctggg atattgtcgt ccagagagtt
901 gggaccaaac tcttcttga caagagagac aactctgact ttgacctct gacagttagt
961 gagactgcca atgagcccc tcaagatgaa ggtaattcct tcaattcacc ccgcaacctg
1021 gccatggagg caacctacat caaccacaat ttctccagc agtgcttgag aatggggaag
1081 gaaagatata acttcccaa cccaacccg ttgtggagg acgacatgga taagaatgaa
1141 atcgctctg ttgcgtaccg ttaccgagg tggaagcttg gagatgatat tgaccttatt
1201 gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc ctcatcaac
1261 atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag
1321 ctggactctc agcagggggc tgcattgcc acggagctga agaacaacag ctacaagttg
1381 gcccgttggg cctgctgtgc ttgtctggct ggatctgagt acctcaagct tggttatgtg
1441 tctcgttacc acgtgaaaga ctctcacgc cagctcatcc taggcacca gcagttcaag
1501 cctaagagt ttccagcca gatcaacctg agcgtggaga atgctgggg cattttacgc
1561 tgcgtcattg acatctgcat gaagctggag gagggcaaat acctcatcct caaggacccc
1621 aacaagcagg tcatccgtgt ctacagcctc cctgatggca cctcagctc tgatgaagat
1681 gagggagaag aggaggagga agaagaggaa gaagaagagg aagaaactta aaccagtgat
1741 gtggagctgg agttgtcct tccaccgaga ctacgagggc cttgatgct tagtggaatg
1801 tgtgtctaac ttgctctcgt acatttagca gatgaaataa aatatatc tgtttagtct
1861 ttaaaaaaaa aaaaaaaaaa a
```

Protein sequence:

```
MAKFMTPVIQDNPSGWGPCAVPEQFRDMPYQPFSKGDRLGKVADWTGATYQDKRYTNKYSSQFGGGSQYAYFHE
EDESSFQLVDARTQKTAYQRNMRFAQRNLRRDKDRRNMLQFNLQILPKSAKQKERERIRLQKKFQKQFQVGRQKW
DQKSQKPRDSSVEVRSDWEVKEEMDFPQLMKMRYLEVSEPQDIECCGALEYDYKAFDRITRSEKPLRSIKRIFHTVT
TTDDPVIRKLAKTQGNVFATDAILATLMSCTRSVYSWDIVVQVRVGSKLFFDKRDNSDFDLTVSETANEPQDEGNSF
NSPRNLAMEATYINHNFSQQCLRMGKERYNFPNPNPFVEDMDKNEIASVAYRYRRWKLGGDDIDLIVRCEHDGVM
GANGEVSFINIKTLNEWDSRHCNGVDWRQKLDLSQRGAVIATELKNNSYKLARWTCCALLAGSEYKLGYSRYHVKD
SSRHVILGTQQFKPNEFASQINLSVENAWGILRCVIDICMKLEEGKYLIKDPNKQVIRVYSLPDGTFSSDEDEEEEEEE
EEEEEEET
```

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X58965. H.sapiens RNA for...[gi:35069]:

H.sapiens RNA for nm23-H2 gene

DNA sequence:

```
1 cggccacgag gcggaatccc ttctgctctc ccagcgcagc gccgcccgcc ggcccctcca
61 gcttcccga ccatggccaa cctggagcgc acctcatcg ccatcaagcc ggacggcgtg
121 cagcgcggcc tggtagggca gatcatcaag cgcttcgagc agaagggaatt ccgcctcgtg
181 gccatgaagt tctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa
241 gaccgacat tctccctgg gctgggaag tacatgaact cagggccggt tgtggccatg
301 gtctgggagg ggctgaacgt ggtgaagaca ggccgagtga tgctgggga gaccaatcca
361 gcagattcaa agccaggcac cattcgtggg gactctgca ttcaggttg caggaacatc
421 attcatggca gtgattcagt aaaaagtgt gaaaaagaaa tcagcctatg gtttaagcct
481 gaagaactgg ttgactacaa gtctgtgct catgactggg tctatgaata agagggtggac
541 acaacagcag tctcctcag cacggcgtgg tgtgtccctg gacacagctc ttcattccat
601 tgacttagag gcaacaggat tgatcattct ttatagagc atattgcca ataaagcttt
661 tggagccgg
```

protein sequence:

```
MANLERTFIAIKPDGVQRGLVGEIIRFEQKGFRLVAMKFLRASEEHLKQHYIDLKDRPFFPGLVKYMNSGPVWAMVW
EGLNVVKTGRVMLGETNPADSKPGTIRGDFCIQVGRNIIHGSDSVKSAEKEISLWFKPEELVDYKSCAHDWVYE
```

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M17885. Human acidic ribo...[gi:190231]:

Human acidic ribosomal phosphoprotein P0 mRNA

DNA sequence:

```
1 cttctctcgc caggcgtcct cgtggaagt acatcgtctt taaacccct cgtggcaatc
61 cctgacgcac cgccgtgatg cccagggaag acagggcgac ctggaagtcc aactacttc
121 ttaagatcat ccaactattg gatgattatc cgaaatgtt cattgtgga gcagacaatg
181 tgggtccaa gcagatgcag cagatccgca tgtccctcg cgggaaggct gtggtgctga
241 tgggcaagaa caccatgatg cgcaaggcca tccgaggga cctggaaaac aaccagctc
301 tggagaaact gctgcctcat atccggggga atgtgggctt tgtgtcacc aaggaggacc
361 tctagtgat cagggacatg ttgtggcca ataagggtcc agctgtgcc cgtgtggtg
421 ccattgccc atgtgaagtc actgtgccag ccagaaacac tggctcggg cccgagaaga
481 cctcctttt ccaggcttta ggtatcacca ctaaaatctc caggggcacc attgaaatcc
541 tgagtgatgt gcagctgatc aagactggag acaaagtggg agccagcgaa gccacgtgc
601 tgaacatgct caacatctcc ccttctcct ttgggtggt catccagcag gtgtcgaca
661 atggcagcat ctacaacct gaagtgttg atatcacaga ggaaacttg cattctgct
721 tcttgagggg tgcgcgaat gttgccagt tctgtctga gattggctac ccaactgtg
781 catcagtagc ccattctatc atcaacgggt acaaacgagt cctggcctg tctgtggaga
841 cggattacac ctccactt gctgaaaagg tcaaggcctt ctggctgat ccatctgcct
901 ttgtggtgct tgcctctgt gctgtgccca ccacagctgc tctgtgct gctgcagccc
961 cagctaaggt tgaagccaag gaagagtcgg aggagtcgga cgaggatatg ggatttggtc
1021 tcttgacta atcaccaaaa agcaaccaac itagccagtt ttattgcaa aacaaggaaa
1081 taaaggctta ctcttt
```

protein sequence:

```
MPREDRATWKSNYFLKIIQLDDYPKCFIVGADNVGSKQMQQIRMSLRGKAVVLMGKNTMMRKAIRGHLENNPALEK
LLPHIRGNVGFVFTKEDLTEIRDMLLANKVPAAARAGAIAPCEVTVPAQNTGLGPEKTSFFQALGITTISRGTIEILSDV
QLIKTGDKVGASEATLLNMLNISPFSFGLVIQQVFDNGSIYNPEVLDITEETLHSRFLGVRNVASVCLQIGYPTVASVP
HSIINGYKRVLALSVETDYTFPLAEKVKAFLADPSAFVAAAPVAAATTAAPAAAAAPAKVEAKEESESEDEDMGFGLFD
```

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X52851. Human cyclophilin...[gi:30167]:

Human cyclophilin gene for cyclophilin

DNA sequence:

```

1  gaattccctt gtaaggtttt cttaacaaaa caccagtcac ataagtgcatt ttattttat
61  atttttgttt atttatttga gacggagctt ctgtctctc aggtcggagt gcagtggcgc
121  catctctgct cgctgcaacc tcacctcctt ggggtccagc gattcctctg cctcagcctc
181  ccgagggggg agctgggact acaggtgcgc accaccatgc ccagctaatt ttgtattttt
241  cgtagagatg ggggttcacc atgtgtcca ggctggctt gaactcctga cctcaggtga
301  tcttccgccc tcggcctccc aaagtgtcgg aattacaggc gtgatccacc gcacccggcc
361  tatttttga gagagggica cactctgtcg tcccggctgg aatgcagtga tgcgatcacc
421  gcccactaca gcctgcacct ccgggctcaa gcaatcctcc ccgcccagcc tctgagtag
481  cgagcgccct gacgcccagc taattttat ttattttat tttttgtag agacggcgctc
541  tctctaagat gcccaggctg gtggccggtg tcgaactcct aagatgaagc gatcctcccc
601  ggccctggcc tcgcgcctc claaagcgcc aggtatgagc caccgcgcct ggcctacaag
661  tgcattttaa ttaaagtatt attaatgtct ttgcctgaag aaattcgctt ttaaattgtg
721  acttatcttt caccacaaaa tcaagcaca attcagcccc gaggcggggg cggtaggagc
781  tggcgggggc gggggcaggg aaagaccagg agcagagatt caaaaagagt aagagggcaa
841  aatgtgcata atgcactctc acaggtgaag gcctggccag gctcctgttt taatggcttc
901  ctctgaaga agattcaagc agagtgaag atatttccg aaagtagagc atttgaaaag
961  cattcataaa tcttcaaaaa ccgagagctg ctctgtccc acctcgtag agaaaacagc
1021  gatgtcaaaa ggcaacctcc ttctgacat tgcttggtag gacgcgacgt ggtgtttgcc
1081  cgcgcggaat gcggacgcaa ggctgtcctt aggtctcggg gacgcgcat cccatttcc
1141  gctcgcggag gcgtagggtc cgggcgcggg accccagtcg acctgactg gcggcgcgac
1201  cttagggcct gcgttcgctt cagttgcccc ctctgtcaa tggggagacg cgcctcatcg
1261  ctgacaacg gccgaagagc cgcgcgctt ccgtctccc cgtgcgcgcg ccatgtctgc
1321  ccccccggt ccgactgac cctccccgt gccccgcgtc cgtactgccc gccccgccc
1381  gactccatg ccgcagcac cgcgacggag ccgcaggcg ggaacctgcc tccgcgctt
1441  agcgcgcacg cgcgcctcat gtgtctctcc catcagcgcc ggctccgtc tataggccag
1501  atgcactgtc actctggcga agtcgcagac ccgattggcc gggacggagg cgcgagaccg
1561  ggttgccggc ggggcccgaac gtgtataaaa acgggcggga ggccaggctc gtgccgtttt
1621  gcagacgcca ccgcccagga aaacctgtga ctattagcca tggtaacccc caccgtgttc
1681  ttgcacattg ccgtcgacgg cgagcccttg ggcgcgctt cctttagggt cgggcggggc
1741  gcggcgctgc ggaatggggc ccagaaaagt ggcgggggtc ggggtgggtg gtacgcccc
1801  aaaggccccg gcgcggggcg accctgctt aggggcgagc gcgggcgggc tgcggcgcca
1861  ttctctgacg aggggccatt ttgggaggtc cgcgagtcgc gggaggaggc cgggacgcgg
1921  cggacaaaag caggcggggc ggctgcgagg ccgttggggg agggggcccg cgtccgccc
1981  ccgcctcat gtggccgcgc cctgtctgt ccgacgcacg tctcggcg cgcgcctcag
2041  gtccgcctt tgagagtcgt gtccgccct agcttggctt gggcgccgca gaccggagcc
2101  agaagcacgc tcgcgggggc ttgcgaccgc ctctctggga agctgtcccc tggcaggcat
2161  ggggtcttta catctgagc tgggaagctg ttgcttagg ggttttctc aaggatcgag
2221  gcggggtgtg agcccgcca tgctcggtcc ttagatccc gggaggccat gttataaaag
2281  gagactgtct gggatgtgac ggggtgccac ttgaaatac ttccatttgg ataaagttag
2341  aatatttata catgtgcccc aaacgtcctt ccgtgtccc ccccccaag cggaaatgtg
2401  aaaatgggccc ttgccttgc ttgtgcccaa ggaaccgctt ccactgcagt gacggcgctg
2461  gcgggggagg gcctcttag ccctcccga ttgtccctt gcctagcaag caagtgtcga
2521  ctggccacaa ggcaggcctc ttccgaccaa ggtggattac cagtattac ctattagt
2581  ttgagagcgt taaatgagt ctaaagatc agttgtaatt atagcatagt atctaaactt
2641  ggcgcgtgtc ttcaaagtta aatattgagt acgattccgt tccagtaac atggatagac
2701  cttagggagt agcgaatatg gatgttagtg gttttattcc tttaaatcac atctcaaaag

```

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2761 gccaccaatg gctagttgg atctattcc gaaaatagat tgatcctcat gcagtctcg
 2821 tgaggacaga gcgatttct tttgcctac cctgtccata gtgcctggca cataggcact
 2881 gaaacactgc atgttaatcc acaccccacc ccacctatga gtgtagicaa agctggtaag
 2941 tgacaagggc ttctgtgaa acttggcctg acctaattgt ggcatcagg ttacccaaag
 3001 agcttcaggg aatgagaaa ggactgcag gcttgatga gaattggagg gtaactgcc
 3061 atgagggctt tggcttagc gaaagtctga aagggaagcc ataggaactt aaacgtaccg
 3121 actataaagc tctgagaaa gctgatgtt tagaaagacc atacattcta ggtacaaata
 3181 cctaaaaact aaaaaataag tacgttggc agggggcg atcacgaagt caggagattg
 3241 agaccatctt gggccctgg tgaaaccca cctctattaa aaatacaaaa attagctggg
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 3481 actagtagtt aattcagcta catcttgaa atagcttata aaatgctact tttaacaag
 3541 ctgttttat gaaaggcct gtaaatgtt atggtattta agtacctct ctgaccataa
 3601 cgtattatac atcaagaaa ggtcaaaac cagatatact agaaaccaat cttttttt
 3661 taccacta ctaggtaagg gcctggatac caagaagtga ctgctatct aatccataa
 3721 gctatgtaa cagattggag gtagtagcat ttctattaca agtgactaaa agaacagctg
 3781 ttaccctg atcgtgcagc agtgctgct gttcctaga atttgcctt gtaagtcta
 3841 gctcaagtg ggggtgtg atagacattt aagaagccat atatctttc agaagtaggt
 3901 gtgatgtact aaaagttga gacacttct agaagctca ctattaaagt tatgactagt
 3961 attgatttt tggcatgtc ttgggttca tgttcttaa cccaactgcc tgcagggcct
 4021 tatggctgc agagcagtt ctgggaatt aaagtaatta ctgaagaagt attctagtga
 4081 gaaaatgaat ttatgactca gaagccccta aagacatgg tactaagcaa caaataagc
 4141 agatgtaat taactgtaat ttctctac agctgttgc agacaaggc ccaaagacag
 4201 cagggtgtc cattttctaa gtttaacaaa gatgtccaa ttgtgacagt ttgtgtgt
 4261 gtgtgtat atatatttt atgtatgtat atatgtgtt aattttttt taaacagaaa
 4321 atttctgct tctgagcact ggagagaaa gatttggta taagggttc tgccttaca
 4381 gaattattcc aggtttatg tgcaggtag gaaattact gaattttat ttattgggt
 4441 tctccctc atttgggatt gagccagaat attcaggat acacatactt gaactgtac
 4501 tctaccattt cggttctatt taaccttct attcagttg aacttgggt taaagttga
 4561 acctgcaga ttggcacac tcatggta tttgtcaga agtgacattt ttctatag
 4621 ttgacagggt ggtgactca cagccataa tggcactgg gcaagtcct tctatggga
 4681 gaaattgaa gatgagaact tcatcctaaa gcatacgggt cctggcatct tgcctatggc
 4741 aaatgctga ccaacacaa atggttccca gttttcatc tgcactgcca agactgagtg
 4801 gtaagggtac aacatggcac actaaccacc tgactaaatg aaaagttgcc ctggggggaa
 4861 cggaacaaac actactttc ttcaacctt gctccacag acttttcat ccctaagata
 4921 ctagaagaag agcatalata aatgacaaat atagccaatg tgatacagaa tgcagatac
 4981 tatgatagaa acttggccct tagctgggtg ttgaattag gtgctactt ttgagatgg
 5041 agtttctc tttgtccagg ttggagtga gtggcacaat ctgggctcac tgcaacctct
 5101 gcctcctgg ttcaagcgt tctctgcct tggcctcctg agtagctgag aatacagatg
 5161 tttgacagca tgcctggcta atttttga tttgttga gacggggtt catcatgtg
 5221 gccaagctgg tctgaactc gtgacttaag gtgaaccacc tgccttggc ccccaaagt
 5281 ctgggattc agcatgagc cactgcgcc aaccaattaa gtgctttt ttttttt
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 5401 gctactgca acctctccc ggttcaagc aattctctg cctcagctc tcaagtagct
 5461 ggaactacag gcatgcacca ccactcccag ctaaatgtg tattattagt agagcggat
 5521 ttaccatgt gtccaggctg gtctgaact cctgggtcct agtgatctg ctgcctgac
 5581 cccccgaag tctgggatt acaggcatga gccactgtc ccaccaatt aagtctgct
 5641 ttatgttac tattaataac atcggttgg ttgggtttt ttttcttg gggttttgt
 5701 ttgtttgt ttgttttg gggaggggg cgcaattcat tctatagt taactcttt
 5761 ttgagatgga gtttctct gtcgccagg ctggagtga gtggcgcat ctggctcac

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5821 tgcaagctcc gcctcccagg ttcacgcat tctctgcct cagcctccc agtagctggg
5881 actataggca catgccacca tgcccggtc atttttgta ttttagtag agacagggtt
5941 tcaccgtgtt agccaggatg gtctgatct cctgacctcg tgatccgcc gccttggcct
6001 cccaaagtgc tgggattaca ggcgtgagcc accgcacccg gcctatatgt gtaactctt
6061 aatggtaat ggagaatcat gttaatgac atttagtaca aaaggctca gtaaaaaaa
6121 aaaaaaaaa gctaccttc tctcttgg tcatgacaca tggaggctgc ttgttggg
6181 ttgccagica taatgattgt tctccttt caaggttga tggcaagcat gtggtgttg
6241 gcaaagtga agaaggcatg aatattgtg aggcctatga gcgcttggg tccaggaatg
6301 gcaagaccag caagaagatc accattgctg actgtggaca actcgaataa gttgacttg
6361 tgttttatct taaccaccag atcattcct ctgtagctca ggagagcacc cctccacccc
6421 atttgctcg agtatcctag aatcttgg ctctcgctgc agtcccttt gggttccatg
6481 tttccttgt tcctcccat gcctagctgg attgcagagt taagttaatg attatgaaat
6541 aaaaactaaa taacaattgt cctcgttga gtttaagtgt gatgtaggct ttatttaag
6601 cagtaatggg ttacttctga aacatcactt gttgcttaa ttctacacag tacttagatt
6661 tttttactt tccagccca ggaagtgtca atgttggg agtgaatat t

protein sequence for Human cyclophilin gene for cyclophilin:

MVNPTVFFDIAVDGEPLGRVSFELFADKVPKTAENFRALSTGEKGFYKGSFHRIPGFMCQGGDFTRHNGTGKSI
YGEKFEDENFILKHTGPGILSMANAGPNTNGSQFFICTAKTEWLDGKHVVFQKVKEGMNIVEAMERFGSRNGKTSKKI
TIADCGQLE

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M12886. Human T-cell rece...[gi:339009]:

Human T-cell receptor active beta-chain mRNA

DNA sequence:

```
1 gtgtgaggcc atcacggaag atgctgtgc ttctgtgt tctggggcta gcaggctccg
61 ggcttggtgc tgtcgtctct caacatccga gctgggttat ctgtaagagt ggaacctctg
121 tgaagatcga gtgccgttcc ctggacttcc aggccacaac tatgttttgg tatcgtcagt
181 tcccgaaaca gagtctcatg ctgatggcaa ctccaatga gggctccaag gccacatacg
241 agcaaggcgt cgagaaggac aagtttctca tcaacatgc aagcctgacc ttgtccactc
301 tgacagtgcag cagtgtccat cctgaagaca gcagcttcta catctgcagt gctagagagt
361 cgactagcga tcaaaaaaat gagcagttct tcggggccagg gacacggctc accgtgctag
421 aggacctgaa aaacgtgttc ccaccgagg tcgtgtgtt tgagccatca gaagcagaga
481 tctcccacac caaaaaggcc acactgggtg gcctggccac aggcctctac cccgaccacg
541 tggagctgag ctggtgggtg aatgggaagg aggtgcacag tggggtcagc acagaccgcg
601 agcccctcaa ggagcagccc gccctcaatg actccagata ctgcctgagc agccgcctga
661 gggctcggc caccttctgg cagaaccccc gcaaccactt ccgctgtcaa gtccagtctt
721 acgggctctc ggagaatgac gagtggaccc aggatagggc caaacctgtc acccagatcg
781 tcagcgccga ggcctggggt agagcagact gtggcttcac ctccgagtct taccagcaag
841 gggctcgtgc tgcaccatc ctctatgaga tcttgctagg gaaggccacc ttgtatgccg
901 tgctggtcag tgcctcgtg ctgatggcca tggtaagag aaaggattcc agaggctagc
961 tcaaaacca tccagggtca ttctcatcc taccaggga ttctcctgta cctgctccca
1021 atctgtgttc ctaaaagtga ttctcactct gcttctcatc tctacttac atgaatactt
1081 ctctctttt tctgtttccc tgaagattga gctccc
```

protein sequence:

```
MLLLLLLLGLAGSGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGV
EKDKFLINHASLTLSTLTVTSAHPEDSSFYICSARESTSDPKNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHT
QKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDQPQLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQ
FYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSAVLVLMAMVKRKDS
RG
```


Figure 12. (Page 13 of 33)M83664. Human MHC class I...[gi:188478]:

Human MHC class II lymphocyte antigen (HLA-DP) beta chain mRNA

DNA sequence:

```

1 agcgagtcct tctttcctg actgcagctc tttcathtt gccatccttc tccagctcca
61 tgatggttct gcaggtttct gcggccccc ggacagtggc tctgacggcg ttactgatgg
121 tgctgctcac atctgtggtc cagggcaggg ccactccaga gaattacgtg taccagggac
181 ggcaggaatg ctacgcgttt aatgggacac agcgcttctt ggagagatac atctacaacc
241 gggaggagta cgcgcgcttc gacagcgacg tgggggagtt ccgggcggtg acggagctgg
301 ggcggcctgc tgcggagtac tggaacagcc agaaggacat cctggaggag aagcgggcag
361 tgccggacag ggtatgcaga cacaactacg agctggacga ggccgtgacc ctgcagcgcc
421 gagtccagcc taagggtaac gtttccccct ccaagaaggg gccctgcag caccacaacc
481 tgctgtctg ccacgtgaca gatttclacc caggcagcat tcaagtcga tggttcctga
541 atggacagga ggaaacagct ggggtcgtgt ccaccaacct gatccgtaat ggagactgga
601 ccttcagat cctggtgatg ctggaaatga ccccccagca gggagacgtc tacatctgcc
661 aagtggagca caccagcctg gacagtcctg tcaccgtgga gtggaaggca cagtctgatt
721 ctgccagag taagacattg acgggagctg ggggcttctg gctggggctc atcatctgtg
781 gagtgggcat ctcatgcac aggaggagca agaaagtca acgaggatct gcataaacag
841 ggttcctgac ctaccgaaa agactaatgt gccttagaac aagcatttgc tgtgtttgt
901 taacacctgg ttccaggaca gaccctcagc ttccaagag gatactgctg ccaagaagtt
961 gctctgaagt cagtttctat cgttctgctc ttgattcaa agcactgttt ctctactgg
1021 gcctccaacc atgttccctt ctcttagca ccacaataa tcaaaaccca acataagtt
1081 ttgcttctt ttaaaaatat gcatcaaac gtctctcatt acttttctt gagggtttta
1141 gtaaacagta ggagttaata aagaagtca ttttggtta cacgtaggaa agaagagaag
1201 catcaaagtg gagatatgtt aactattgta taatgtggcc tgtatacat gacactctc
1261 tgaattgact gtaattcagt gagctgcccc caaatcaagt ttagtgcct catccattta
1321 tgtctcagac cgctattctt aactattcaa tggtagcag actgcaaac tgcctgatag
1381 gacctatatt cccacagcac taattcaaca tatacttac tgagagcatg tttatcatt
1441 accattaaga agttaaatga acatcagaat taaaatcat aatataatc taatacact
1501 t

```

protein sequence:

```

MMVLQVSAAPRTVALTALLMVLTSVVQGRATPENIVYQGRQECYAFNGTQRFLERYIYNREEYARFDSVDVGEFRAV
TELGRPAAEYWNSQKDILEEKRAVPDRVCRHNYELDEAVTLQRRVQPKVNVSPSKKGPLQHHNLLVCHVTDFYPGSI
QVRWFLNGQEETAGVVSTNLIRNGDWTFQILVMLEMTQQGDVYICQVEHTSLDSPVTVEWKAQSDSAQSKTLTGA
GGFVLGLIICGVGIFMHRRSKKVQRGSA

```

Figure 12. (Page 14 of 33)D83779. Human mRNA for KI...[gi:1228040]

Human mRNA for KIAA0195 gene, complete cds

```

1  cggacatggc tgcggccccc ggaggagggg acgtgaagtg aggagggggg tgggagggga
61  gaggacgagg gcgaggaaga ccagccccgg gggcccgatg ttgtgactgt gacagactca
121 ctgggggttg tacatgctgg ggaggagcct tccttcagg ggtgaccaca ttcactggg
181 catgcctgca gtactcttgg cccatggacc tgaaggagaa gcacctgggc gagcctccct
241 cagccctggg cctgtccacg cggaaggccc tcagcgtcct gaaggagcag ctggaggcag
301 tgctggaagg acatctcagg gaggcgaaga agtgtctgac gtggaaggag gtgtggagaa
361 gcagcttctt ccaccacagt aaccgctgct cctgctcca ctggccgggg gcctactca
421 tgctactggc cgtgctgctg ctgtggggt gctcggggg acagccagcc gggagccgtg
481 ggggtggggt gggaatgcc tcggccttgt tctgttact gcttcaac ctgtgctca
541 tcgggcggca agaccggctg aagcgtcggg aggtagagcg gaggtgcga gggatcattg
601 accaaatcca agatgccctc agggatggca gggagatcca gtggcccagt gccatgatac
661 cagacctcca catgcctttt gcgccatctt ggtccttgca ctgggcctac agagacggac
721 acctggtcaa cctgccagtc agcctgctgg ttgaaggaga catcatagct ttgaggcctg
781 gccaggaatc gttgtctct ctgaggggga tcaaggatga cgagcacatc gtctggagc
841 cgggagacct ctccccccc ttctccctc caccctcacc ccggggagaa gtggagagag
901 ggccacagag cccccagcag caccggcttt tccgtgtcct tgagaccctt gtgattgaca
961 acatcagatg gtgcctggac atggccctgt ccgaccagct cactgccctg gacaatgagc
1021 gggtcacagt gcagtcggtg atgtacact atgtgtgcc cgtgtcctg gccggcttc
1081 tcatcaccaa tgcctgcgc ttcacttca gtgccccggg ggtcacttc tggcagtaca
1141 cctctctcca gctccagggt aatggcgctc tgcctatctt cccctgtct ttccagtcc
1201 tctgggttct ggcaactgcc tgtggagagg cccgtgtcct ggccagatg agcaaggcct
1261 caccagctc cctgctggtt aagtctcag aggtactct cagcagctat acggaggctg
1321 tctctctca ggaatgctg cgtgcattt ggggccactt cctgagggtg ctggggggga
1381 catgccaaac gctgagccac agtccagcc tctgcacag cctgggctct gtcacggtcc
1441 tgtgtgtgt ggacaaacag gggatcctgt catggccaaa tccagccca gagactgtac
1501 tgttctcag cggaagggtg gagccccctc acagcagcca tgaggacctc accgatggcc
1561 tatccacccc ctctctgc catcccgagc cccatgaacg agacgccctc ctggctggct
1621 cctgaacaa caccctgcac cttccaatg agcaggagcg tggcgactgg cctggcgagg
1681 ctccaagcc ccccgagccc tatcacacc acaaagcgca tggccgcagc aaacacccat
1741 ctggctcaa cgtgagcttc agcagggaca ccgagggttg tgaagaagag cccagcaaga
1801 cccagcctgg gatggagagc gaccctacg aagcagagga cttgtgtgt gactaccacc
1861 tggagatgct gagcctgtcc caggaccagc agaaccctc ctgcatccag ttgatgact
1921 ccaactggca gctgcacctc acctccctca aaccctggg cctcaatgtg ctgctgaacc
1981 tgtgtgatgc cagcgtcacc gagcgctgt gccgattctc cgaccacctg tgcaacattg
2041 cctgcaaga gagccacagc gccgtgctgc ccgtccatgt gccctggggc ctctgcgagc
2101 ttgcccctt cattggcttc actcctggg ccaaggagct ttcaagcag gagaaccatc
2161 tggcgctgta ccgctcccc agtgcgaga caatgaagga gacatcgctg gggcggtct
2221 cctgtgtcac caagcgcgg cctccctca gccacatgat cagcctcttc attaaagaca
2281 ccaccaccag cacagagcag atgtgtccc atggaccgc tgatgtgtc ttagaggcct
2341 gcacagactt ctgggacgga gctgacatct acctctctc gggatctgac agaaagaaag
2401 tctgtgactt ctaccagcga gcctgcctgt ctgggtattg ctctgcctc gcctacaagc
2461 ccatgaactg gcgccgttc tctcagctca atggcaagt catcgagctg gtacagggtc
2521 ccggccaaag cagcatctc accatgtgcg agctgccag caccatcccc atcaagcaga
2581 acgcccgcg cagcagctgg agctgtgacg aaggatcgg ggagggtctg gagaaggaag
2641 actgcatgca ggccctgagc ggccagatct tcatgggcat ggtgtcctcc cagtaccagg
2701 cccggctgga catcgtgcgc ctcatgtatg ggctgtcaa cgctgcac cgtttgtct
2761 acttctctt ggaggatgag ctcaaaagca aggtgttgc agaaaaaatg ggctggaga

```

Figure 12. (Page 15 of 33)

2821 caggctggaa ctgccacatc tccctcacac ccaatggtga catgcctggc tccgagatcc
 2881 cccctccag cccagccac gcaggctccc tgcagatga cctgaatcag gtgtcccgag
 2941 atgatgcaga agggctctc ctcatggagg aggaggcca ctggaccctc atcagctcc
 3001 agcctacgga cagcgacatc cccagcttcc tggaggactc caaccgggcc aagctgcccc
 3061 ggggtatcca ccaagtgcgg cccacctgc agaacattga caacgtgccc ctgctagtgc
 3121 ccttttcac cgactgcacc ccagagacca tgtgtgagat gataaagatc atgcaagagt
 3181 acggggaggt gacctgctgc ctgggcagct ctgccaacct gcggaacagc tgcctctcc
 3241 tccagagcga catcagcatt gccctggatc ccctgtacc atcccgttc tctggggaga
 3301 ccttggcta cgccaccagc atcagcatgg cccaggcctc ggatggcctt tctcccctgc
 3361 agctgtcagg gcagctcaac agcctgccct gttccctgac ctttgcag gagagacca
 3421 tcagcatcat ccggtctatc gaacaggctc ggcatgccac ctatggcatc cgtaagtgt
 3481 tctcttctc gtgcagtgc cagctgactc ttgtgtcat ccagttcctt tcttgctgg
 3541 tccagctgcc gccactcctg agtaccaccg acatcctgtg gctgtcctgc tttgtacc
 3601 ctctgtcag catctctctg ctggggaagc ccccatag ctccatcatg tctatggaa
 3661 cggggaaaaa cctccagtc attccaaga agaccagca ctacttctg ctctgttcc
 3721 tgctcaagtt cagctcacc atcagctcct gccatctg ctttggctc acactgcaga
 3781 gttctgtga cagctccgg gaccgcaacc tcaccaactg ctctcctgc atgctgcca
 3841 gcaacgacga cagggtcca gccgtgttg aggacttgc caatggactg ctgtcgctc
 3901 agaagctcac ggccgccctg attgtcctgc acactgtct cattccatc acccatgtc
 3961 atcgaccaa gccctgttg agaaagagcc ccttgacaa cctctgttg gccgtgacag
 4021 tgcctgtgt gtgtcgttg cagggtgtc agacgctgt ggacctgcag ctgtggacac
 4081 acagggacag ccacgtccac ttggccttg aggacgtgc cctgtgaca tggctcctg
 4141 gctgcctgc cctgtcctt gtgtgtgtga ccaatgagat cgtgaagta catgagattc
 4201 ggttccgagt ccgtaccag aagcgacaga agctgcagtt tgaactaag ctgggcatga
 4261 actctccct ctgagccact ggctgtgtg gctgtagt ccccgctcc tgggctaaa
 4321 gccagacca ttctgaaca ggggagttg tatcatgaat gtctcaggt ttgtcctgc
 4381 accgtggca ctggaaaccc agtccccgt gtcagaccc gctgtctcc tgagccctg
 4441 ggctactgt ggaggagct acggcctgg cccttgcca gtcctggctc tccctgggc
 4501 ctaccaggg acactctga atgtatggc tcaggcgctc cctagagggg cctaaaccc
 4561 cctaccctgt gagctacccc cttaggat ccctgcccc ctggagatc cctgcccc
 4621 cagtgcctt gctcgtggg ccctggacac ggcctgaag ccaacctct ttggaggagc
 4681 aacagcagca gcctggccg acgctcaa ctccaaggc tgccgtggag ggcaggggg
 4741 tggctgtgc ctggtgtg ccccgagtc cccctccc tccctctg gggagctc
 4801 ccgctgaac ctgaagatg agcagggccc ccgttcgccc ctggagcctc ttcctgtcc
 4861 tggctaacg tggctgctg tcagtctgg ggaatctgc ccaggtctc tcagcctg
 4921 cccagttct gggagaagt tctactgtg tatatttt actggaaatg agccttttag
 4981 gaatgaatg agactggtt gattaaaaat gtgtcaattg ct

Figure 12. (Page 16 of 33)

Protein sequence of Human KIAA0195

MDLKEKHLGEPPSALGLSTRKALSVLKEQLEAVLEGHLRERKKC
LTWKEVWRSSFLHHSNRCSCFHWPGASLMLLAVLLLLGCCGGQPAGSRGVGLVNASAL
FLLLLLNLVLIGRQDRLKRREVERRLRGIIDQIQDALRDGREIQWPSAMYPDLMHPFA
PSWSLHWAYRDGHLVNLVPVLLVEGDIIALRPGQESFASLRGIKDDHIVLEPGDLFP
PFSPPSPRGEVERGPQSPQQHRLFRVLETPVIDNIRWCLDMALSRPVTALDNERFTV
QSVMLHYAVPVVLGFLITNALRFIFSAPGVTSWQYTLLQLQVNGVLPILPLLFPVLW
VLATACGEARVLAQMSKASPSSLLAKFSEDTLSSYTEAVSSQEMLRCIWGHFLRVLGG
TSPTLSHSSSLLHSLGSVTVLCCVDKQGILSWPNPSPETVLFFSGKVEPPHSSHEDLT
DGLSTRSFCHPEPHERDALLAGSLNNTLHLSNEQERGDWPGEAPKPPEPYSHHKAHGR
SKHPSGSNVFSRDTEGEEEPSKTQPGMESDPYEAEDFVCDYHLEMLSLSQDQQNPS
CIQFDDSNWQLHLTSLKPLGLNVLLNLCDASVTERLCRFSDHLCNIALQESHSAVLPV
HVPWGLCELARLIGFTPGAKELFKQENHLALYRLPSAETMKETSLGRLSCVTKRPPPL
SHMISLFIKDTTSTEQMLSHGTADVLEACTDFWDGADIYPLSGSDRKKVLDIFYQRA
CLSGYCSAFAYKPMNCALSSQLNGKCIELVQVPGQSSIFTMCELPSTIPIKQNARRSS
WSSDEGIGEVLEKEDCMQALSGQIFMGMVSSQYQARLDIVRLIDGLVNACIRFVYFSL
EDELKSKVFAEKMGLTGWNCISLTPNGDMPGSEIPPSSPSHAGSLHDDLNQVSRDD
AEGLLLMEEEGHSDLISFQPTDSDIPSFLEDSNRAKLPRGIHQVRPHLQNDNVPLL
PLFTDCTPETMCEMIKIMQEYGEVTCCLGSSANLRNSCLFLQSDISIALDPLYPSRCS
WETFGYATSI SMAQASDGLSPLQLSGQLNSLPCSLTFRQEETISIIRLIEQARHATYG
IRKCFLLQCQLTLVVIQFLSCLVQLPPLLSTTDILWLSCFCYPLLSISLLGKPPHS
SIMSMATGKNLQSIPKKTQHYFLLCFLLKFSLTISSCLICFGFTLQSFCDSSRDRLT
NCSSVMLPSNDDRAPAWFEDFANGLLSAQKLTAALIVLHTVFISITHVHRTKPLWRKS
PLTNLWWAVTVPVVLLGQVVQTAVDLQLWTHRDSHVHFGLEDVPLLTWLLGCLSLVLV
VVTNEIVKLHEIRVRVRYQKRQKLQFETKLG MNSPF

Figure 12. (Page 17 of 33)**L36719. Homo sapiens MAP ...[gi:685173]****Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds**

```

1  tggctggcaa tggccttgct gacctgagc cgggcccacg tggggacctt tggagcacag
61  cctacgatcc tggtgcaagg ccggtggatg cagaggccag tccatatacc acccaggcct
121  gcgaggagcg tggccccac ccatccagcc catatgtgca agtgcccttg acagagaggc
181  tggtcataat catgttgacc atttatgggc cacaacaggt ccccatctgc gcagtgaacc
241  ctgtgtgag caccttgacg acgtgatctt gcttctctc gcagcactgt gcggggcagg
301  aaaatccaag aggaagaagg atctacggat atcctgcatg tccaagccac ccgcacccaa
361  cccacacccc ccccggaacc tggactcccg gaccttcac accattggag acagaaactt
421  tgagggtggag gctgatgact tggtgacat ctcagaactg ggccgtggag cctatggggt
481  ggtagagaag gtgcggcacg ccagagcgg caccatcatg gccgtgaagc ggatccgggc
541  caccgtgaac tcacaggagc agaagcggct gctcatggac ctggacatca acatgcgcac
601  ggtcgactgt ttctacactg tcaccttcta cggggcacta ttacagagg gagacgtgtg
661  gatctgcatg gagtcatgg acacatcctt ggacaagtc taccggaagg tgcgtgataa
721  aaacatgaca attccagagg acatccttgg ggagattgct gtgtctatcg tgcgggcctt
781  ggagcatctg cacagcaagc tgcgggtgat ccacagagat gtgaagccct ccaatgtcct
841  tatcaacaag gagggccatg tgaagatgtg tgactttggc atcagtggtt acttggtgga
901  ctctgtggcc aagacgatgg atgccggctg caagccctac atggcccctg agaggatcaa
961  ccagagctg aaccagaagg gctacaatgt caagtccgac gtctggagcc tgggcatcac
1021 catgattgag atggccatcc tgcggttccc ttacgagtcc tgggggaccc cgttccagca
1081 gctgaagcag gtggtggagg agccgtcccc ccagctccca gccgaccgtt tctccccga
1141 gtttgtggac ttactgtctc agtgccctgag gaagaacccc gcagagcgta tgagctacct
1201 ggagctgatg gagcaccctt tcttcacctt gcacaaaacc aagaagacgg acatgtctgc
1261 ctctgtgaag aagatcctgg gagaagactc ataggggctg ggccctggac cccactccgg
1321 cctccagag cccacagcc ccatctgcgg gggcagtgtc cccacacacc ataagctact
1381 gccatcctgg cccagggcat ctgggaggaa ccgagggggc tgctcccacc tggctctgtg
1441 gcgagccatt tgtcccaagt gccaaagaag cagaccattg gggctcccag ccaggccctt
1501 gtgcggccca ccagtgcctc tcctgtctgc tcctaggacc cgtctccagc tgcgtgagtc
1561 ctggactgag ggggccttga tgcccctgt ggatgtctgt gccctgcac agcaggctgc
1621 cagtgcctgg gtggatgggc caccgccttg cccagcctgg atgccatcca agttgtatat
1681 tttttaatc tctgactga atggactttg cacactttgg cccaggggtg ccacacctt
1741 atccggcctt tggtgcgggg tacacaagag gggatgagtt gtgtgaatac cccaagactc
1801 ccatgaggga gatgccatga gccgccaag gcctcccct ggactggca aacagggcct
1861 ctgcggagca cactggctca cccagtctg cccgccaccg ttatcgggtg cattcacctt
1921 tcgtgtttt ttaatttat cctctgtga tttttctt tgccttatgg gtttgcttg
1981 ttttcttg atggtttga gctgatcgt tctccccac ccctagggg

```

Protein sequence of Homo sapiens MAP kinase kinase 3 (MKK3)

```

MSKPPAPNPPTPRNLDSTRTITIGDRNFEVEADDLVTISELGRG
AYGVVEKVRHAQSGTIMAVKRIRATVNSQEQKRLMDLDINMRTVDCFYTVTFYGALF
REGDVWICMELMDTSLDKFYRKVLDKNMTIPEDILGEIAVSIVRALEHLHSLSVIHR
DVKPSNVLINKEGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINPELNQKGYNV
KSDVWSLGITMIEMAILRFPYESWGTPFQQLKQVVEEPSQLPADRFSPFVDFTAQC
LRKNPAERMSYLELMEHPFFTLHKTKKTDIAAFVKILGEDS

```

Figure 12. (Page 18 of 33)**U47634. Human beta-tubuli...[gi:1297273]****Human beta-tubulin class III isotype (beta-3) mRNA, complete cds**

```
1 atgctgggaga tcgtgcacat ccaggccggc cagtgcggca accagatcgg ggccaagttc
61 tgggaagtca tcagtatga gcatggcatc gacccagcg gcaactacgt gggcgactcg
121 gacttcgagc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg
181 cctcgagcca ttctggtgga cctggaaccc ggaaccatgg acagtgtccg ctacggggcc
241 ttggacatc tcttcaggcc tgacaatttc atcttggtc agagtggggc cggcaacaac
301 tgggccaagg gtcactacac ggagggggcg gagctggtg attcggctct gtagtgggtg
361 cggaaggagt gtgaaaactg cgactgcctg cagggcttcc agctgacca ctgcctgggg
421 ggggggacgg gctccggcat gggcacgtg ctatcagca aggtgcgtga ggagtatccc
481 gaccgcatca tgaacacctt cagcgtcgtg cctcaccca aggtgtcaga cacggtgggtg
541 gaaccctaca acgccacgct gtccatccac cagctggtg aaaacacgga tgaacctac
601 tgcctcgaca acgaggcgct ctacgacatc tgcttcgca cctcaagct ggccacgccc
661 acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cactccttg
721 cgcttccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc
781 ccgcgcctgc acttcttcat gcccggttc gccccctca ccaggcgggg cagccagcag
841 taccgggccc tgacctgcc cgagctcacc cagcagatgt tcgatgcaa gaacatgatg
901 gccgcctcgc acccgcgcca cggccgctac ctgacggtg ccaccgtgtt ccggggccgc
961 atgtcatga aggaggtgga cgagcagatg ctggccatcc agagcaagaa cagcagctac
1021 ttctggagt ggtaccccaa caactgaag gtggcgtgt gtgacatcc gccccgggc
1081 ctcaagatgt cctcacctt catcggaac agcacggcca tccaggagct gttcaagcgc
1141 atctccgagc agttcacggc catgttccgg cgcaaggcct tctgcactg gtacacgggc
1201 gagggcatgg acgagatgga gttaccggag gccgagagca acatgaacga cctggtgtcc
1261 gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatga cgaagacgac
1321 gagggaggat cggaggccca gggcccaag tgaactgct cgcagctgga gtgagaggca
1381 ggtggcggcc ggggccaag ccagcaggt ctacaccccc ggagccatct tgctccgac
1441 accctgctt cccatcgcc ctagggtcc ctgcccgc tctgcagta ttatggcct
1501 cgtctcccc cactaggcc acgtgtgagc tgctcctgc tctgtctat tgcagctcca
1561 ggcctgacgt ttacgggtt tgtttttac tggtttgtt ttatatttc ggggatactt
1621 aataaatcta ttgctgtcag ataccctt
```

Protein sequence of Human beta-tubulin class III isotype (beta-3)

```
MREIVHIQAGQCGNQIGAKFWEVISDEHGDPSGNYVGSDSLQL
ERISVYYNEASSHKYVPRAILVDLEPGTMDSVRSGAFGHLFRPDNFIQSGAGNNWA
KGHYTEGAELVDSVLDVVRKECENCDCLOQFQLTHSLGGGTGSGMGTLLISKVREEYP
DRIMNTFSVVPSPKVS DTVVEPYNATLSIHLQVENTDETYCIDNEALYDICFRTLKLA
TPTYGDLNHLVSATMSGVTTSLRFPGLNADLRKLAVNMVFPRLHFFMPGFAPLTRR
GSQQYRALTVPELTQQMFDANKMMAACDPRHGRYLT VATVFRGRMSMKEVDEQMLAIQ
SKNSSYFVEWIPNNVKVAVCDIPPRGLKMSSTFIGNSTAIQELFKRISEQFTAMFRRK
AFLHWYTGEGMDEMEFTEAESNMNDLVSEYQQYQDATAEEEGEMYEDDEESEAQGP
```

Figure 12. (Page 19 of 33)M19267. Human tropomyosin...[gi:339943]

Human tropomyosin mRNA, complete cds

```

1  cagaatctcc ggcagtttt gtacctcaag aagtaagtgg aacaccttc cctgtcatag
61  ttatttcat ccagacatct ggtggaagca tcagattcct tacagatata agagagggcat
121 catttaaaag gtagaacagg atcgacaaac aaggatttat gtcaggatct ctacagcctct
181 gtgtaccga gggcatttct aacagtcttc ttactacggc ctccgccgac cgcgcgctcg
241 ccccgccgct cctgtctcag cccaggggcc cctcgccgcc gccaccatgg acgccatcaa
301 gaagaagatg cagatgtcga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc
361 ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg agctggtgtc
421 actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa
481 agatgcccgag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt
541 agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg cccaggagcg
601 tctggcaaca gcttgcaga agctggagga agctgagaag gcagcagatg agagtgagag
661 aggcataaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga
721 gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaaat atgaagaggt
781 ggcccgtaa gctgtcatca ttgagagcga cctggaacgt gcagaggagc gggctgagct
841 ctcaagaagg caagtccgac agctggaaga acaattaaga ataatggatc agacctgaa
901 agcattaatg gctgcagagg ataagtactc gcagaaggaa gacagatatg aggaagagat
961 caaggtcctt tccgacaagc tgaaggagc tgagactcgg gctgagtttg cggagaggtc
1021 agtaactaaa ttggagaaaa gcattgatga cttagaagag aaagtggctc atgccaagaa
1081 agaaaacctt agtatgcac agatgctgga tcagacttta ctggagttaa acaacatgtg
1141 aaaacctcct tagctgcgac cacattctt cattttgtt tgtttgtt tgttttaaa
1201 cacctgcta ccccttaaat gcaatttat tactttacc actgtcacag aaacatccac
1261 aagataccag ctaggtcagg gggtggggaa aacacataca aaaagcaagc ccatgtcagg
1321 gcgatcctgt tcaaatgtg ccatttccc ggttgatgct gccacactt gttagagagt
1381 tagcaacaca gtgtgcttag tcagcgtagg aatcctcact aaagcaggag aagtccatt
1441 caaagtgcc aatgatagat caacaaggaa ggtaaatgtt ggaaacacaa tcagggtgtg
1501 attggtgcta cttgaacaa aaggcccc tgtggtctt tgttaacat tgtacaatgt
1561 agaactctgt ccaacactaa ttattttgt ctgagtttt actacaagat gagactatgg
1621 atcccgcatg cct

```

Protein sequence of Human tropomyosin

```

MDAIKKKMQMLKLDKENALDRAEQAEADKKAEDRSKQLEDELV
SLQKKLKGTEDELDKYSEALKDAQEKLAEKKATDAEADVASLNRRRIQLVEEELDRA
QERLATALQKLEEAKEADESERGMKVIESRAQKDEEKMEIQEIQLKEAKHIAEDADR
KYEEVARKLVIESDLERAEEAELSEGQVRQLEEQLRIMDQTLKALMAAEDKYSQKE
DRYEEEEIKVLSDKLKEAETRAEFAERSVTKLEKSIDDLEEKVAHAKEENLSMHQMLDQ
TLLELNNM

```

Figure 12. (Page 20 of 33)S78798. 1-phosphatidylinositol...[gi:1042033]

1-phosphatidylinositol-4-phosphate 5-kinase isoform C [human, peripheral blood leukocytes, mRNA, 1835 nt]

```

1 ttacacttta tacttccggc tcgaatattg tgtggaattg tgancggata acaatttcac
61 acaggaaaca nctatgacct tgattacgcc aagctcgaaa ttaacctca cttaaaggaa
121 caaaagctgg agctcgcgcg cctgcaggtc gacactagt gatccaaaga attcggcacg
181 aggcgacggg cggagcggag cgcggcgcgc cggggccgcc gccgggggga tcggtgcct
241 ccccgggccg ggtgtagaga gggcggtcc cggcctcgg gagcacggcg gtggagggga
301 cataggaggc ggccatggcg accccggca acctagggtc ctccgtctg gcgagcaaga
361 ccaagaccaa gaagaagcac ttctagcgc agaaagtga gctgttcgg gccagcgacc
421 cgctgctcag cgtcctcatg tggggggtaa accactgat caatgaactg agccatgttc
481 aaatccctgt tatgtgatg ccagatgact tcaaagccta tcaaaaata aaggtggaca
541 atcacctttt taacaaagaa aacatgccga gccattcaa gtttaaggaa tactgcccga
601 tggcttccg taactcggg aagaggttg gaattgatg tcaagattc cagaattccc
661 tgaccaggag cgcacccctc cccaacgact ccaggcccg cagtggagct cgttttaca
721 ctctctacga caaaagatac atgatcaaga ctattaccag tgaagacgtg gccgaaatgc
781 acaacatctt gaagaaatac caccagtaca tagtggatg tcatgggatc accctcttc
841 cccacttgtt gggcatgtac cggctaatg ttgatggag tgaatatat gtgatagta
901 caagaaatgt attcagccac cgttgtctg tcataggaa atacgacta aagggtcta
961 cagtggctag agaagctagt gacaaagaaa agccaaaga actgccaact ctgaaagata
1021 atgatttcat taatgaggc caaaagattt atattgatg caacagcaag aaggtcttc
1081 tggaaaaact aaaaaaggat gttgagttc tggccagct gaagctcatg gactacagtc
1141 tgctgggtgg aattcatgat gtggagagag ccgaacagga ggaagtggag tgtgaggaga
1201 acgatgggga ggaggagggc gagagcgtg gcacccaccc ggtgggaacc cccccagata
1261 gccccgggaa tactatgaac agtcaccac ccttggtcc cggggagttc gagccgaaca
1321 tcgacgtcta tggaaattaag tgccatgaaa actcgcttag gaaggaggtg tacttcatgg
1381 caattattga catccttact cattatgat caaaaaagaa agctgcccat gctcaaaaa
1441 ctgttaaaca tggcgtggc gcggagatct ccacgtgaa ccagaaacag tattcaaagc
1501 gctttttgga cttattggc cacatctga cgtaacctc tgcgcayctc ggacagcatg
1561 aacattggat ggacagaggt ggctcggg taggaaaaat gaaaaccaa ctactgaag
1621 tactcatctt gcaggaagca aacctcctt ttacatctt caggccaaga tgactgatt
1681 gggggctact cgctttacag ctacctgatt tcccagcat cgttctagct atttctgact
1741 ttgtgtatat gtgtgtgtgt gtgtgtggg ggggggtgag tgtgtgccc cggtgtgcat
1801 taaagcataa attaatataa cagccactc ggtca

```

Protein sequence of 1-phosphatidylinositol-4-phosphate 5-kinase isoform C

```

MATPGNLGSSVLASKTKTKKKHFVAQKVLFRA SDPLLSVLMWG
VNHSINELSHVQIPVMLMPDDFKAYSKIKVDNHLFNKENMP SHFKFKEYCPMVFRNCG
KRFGIDVQDFQNSLTRSAPLPNDSQARSGARFHTSYDKRYMIKTITSEDVAEMHNILK
KYHQYIVECHGITLLPHLLGMYRLNVDGVEIYVIVTRNVFSHRLSVYRKYDLKGSTVA
READSKEKAKELPTLKDNDFINEGQKIYIDDNSKKVFLEKLKKDVEFLAQLKLM DYSL
LVGIH DVERAEQEEVECEENDGEEGESD GTHPVGTPPDSPGNTLNSSPPLAPGEFEP
NIDVYG ICHENS PRKEVYFMAIIDILTHYDAKKKAAHAAKTVKHGAGAEISTVNPEQ
YSKRFLDFIGHILT

```


Protein sequence of Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1
MAPKKPEPKKEAAKPAPAPAPAPAPAPAPEAPKEPAFDPKSV
KIDFTADQIEEFKEAFSLFDRTPPTGEMKITYGQCGDVLRLALGQNPTNAEVLRLVLGKPK
PEEMNVKMMLDFETFLPIQLHISRNEKGTYEDFVEGLRVFDKESNGTVMGAELRHVLA
TLGEKMTAEAEVEQLLAGQEDANGCINYEAFVKHMSG

Figure 12. (Page 22 of 33)X90999. H.sapiens mRNA fo...[gi:1237212]

H.sapiens mRNA for Glyoxalase II

```
1 gatttgcgga agaacctgac cgtggacgag ggcaccatga aggtagaggt gctgcctgcc
61 ctgaccgaca actacatgta cctggtcatt gatgatgaga ccaaggaggc tgccattgtg
121 gatccggtgc agcccagaa ggtcgtggac gcggcgagaa agcacggggt gaaactgacc
181 acagtgtca ccaccacca ccactgggac catgctggcg ggaatgagaa actggtaag
241 ctggagtgg gactgaaggt gtacgggggt gacgaccgta tcggggccct gactcacaag
301 atcactcacc tgtccacact gcaggtggg tcttgaacg tcaagtgcct ggcgaccccg
361 tgccacactt caggacacat ttgttacttc gtgagcaagc ccggagggtc ggagccccct
421 gccgtgttca caggtgacac ctgtttgtg gctggctgcg ggaagttcta tgaagggact
481 gcgcatgaga tgtgtaaagc tctgctggag gtcttgggcc ggctcccccc ggacacaaga
541 gtctactgtg gccacgagta caccatcaac aacctcaagt ttgcacgcca cgtggagccc
601 ggcaatgccg ccatccggga gaagctggcc tggccaagg agaagtacag catcggggag
661 cccacagtgc catccacct ggcagaggag ttacctaca accccttcat gagagtgagg
721 gagaagacgg tgcagcagca cgcaggtgag acggacccgg tgaccacat gcgggcccgtg
781 cgcagggaga aggaccagtt caagatgcc cgggactgag gccgccctgc acctcagcg
841 gatttggga ttaggctct ttagtaact ggcttctg ctgtccgtg cgggaaattc
901 agtctgatt taacctaat ttacagccc ttggctgtg ttatcgga ttctaatgca
961 tattataag agaagttta caagtatta ttccataaa aaaaaaaaaa a
```

Protein sequence of H.sapiens mRNA for Glyoxalase II

```
MKVEVLPALTDNYMYLVIDDETKEAAIVDPVQPQKVVDAAARKHG
VKLTTVLTTTHHHWDHAGGNEKLVKLESGLKVYGGDDRIGALTHKITHLSTLQVGSINV
KCLATPCHTSGHICYFVSKPGGSEPPAVFTGDTLFVAGCGKFYEGTADCKALLEVL
GRLPPDTRVYCGHEYTINNLFARHVEPGNAAIKELAWAKEKYSIGEPTVPSTLAE
FTYNPFMRVREKTVQQHAGETDPVTTMRAVRREKDKQKMPRD
```

Figure 12. (Page 23 of 33)**AF027515. Homo sapiens tran...[gi:2772909]****Homo sapiens trans-golgi network glycoprotein 48 (TGN) mRNA**

```

1 agaggggccc gcgcgcgga tctcgcgaga gcattagagg gcggaagcgc tatccgagca
61 ggatgcggtt cgtggtgcc ttggtctcc tgaacgtcgc agcggcgga gccgtgccgc
121 tcttgccac cgaagcgtc aagcaagaag aagctggagt acggccttct gcaggaaacg
181 tctccacca cccagcttg agccaacggc ctggaggctc taccaagtcg catccggagc
241 cgcagactcc aaaagacagc cctagcaagt cgagtgcgga ggcgcagacc ccagaagaca
301 ccccaacaa gtcgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtcgggtg
361 cggaggcaca gaccccaaa ggcagcacta gcaagtcggg ttcggaggcg cagaccacaa
421 aagacagcac tagtaagtcg catccggagc tgcagactcc aaaagacagc actggcaaat
481 cgggtgcgga ggcgcagacc ccagaagaca gcccacacag gtcgggtgcg gagccaaaga
541 cccaaaaaga cagccctagc aagtcaggtt cggaggcgca gaccacaaa gatgtcccta
601 ataagtcggg tgcggcggc cagaccccaa aagacggctc cagcaagtcg ggtgcggagg
661 atcagacccc aaaagacgtc ctaacaagt cgggtgcgga gaagcagact ccaaagacg
721 gctctaaca gtcgggtgca gaggagcagg gcccaataga cgggccagc aagtcgggtg
781 cggaggagca gacctcaaaa gacagcccta acaagggtgt tccagagcag ccttcccgga
841 aagaccattc caagccatc tccaaccctt ctgatacaa ggagctcccc aaggctgaca
901 caaaccagct tgctgacaaa ggaagcttt ctctcatgc ttcaaaaacc gaatctgggg
961 aggaaactga cctcattct ccccgagg aggaagttaa gtctcagag cctactgagg
1021 atgtggggcc caaagaggct gaagatgatg atacaggacc cgaggagggc tcaccgccc
1081 aagaagagaa agaaaagatg tccggttctg cctccagtga gaaccgtgaa gggacacttt
1141 cggattccac gggtagcgag aaggatgacc ttatccgaa cggttctgga aatggcagcg
1201 cggagagcag ccactcttt gcatactgg tgactgcagc cattcttg gctgtcctt
1261 atatgccta tcacaacaag cgaagatca ttgctttgt cctggaagga aaaagatcta
1321 aagtcacccg gcggccaaag gccagtact accaacgtt ggaccagaag atctttctc
1381 cccaagtc taacagaatg gtatattct ctggaaaaag atgaacgtc caatggatt
1441 gtgctgctc cgttcagct ttgattttt tgccttgag aacctgtcc tcctgctga
1501 tttgttcta aatcaaaaaga atgaagaaa aaagtactgt gacctgagag acaccctct
1561 ctgaattta gtggcgggc tgggtggca gaggtagggg gctgcttgg gcttgcacc
1621 tgcacttgg tgacattgt cttctgtt cctttattt atgctggtg cttccatcg
1681 ttctctctg gggtagtg aggggtatat ggaacacgg ctatgacaa agggagatcc
1741 cagcctggc agcctgcgt gctgaccacc ctccctggg cccgggctct gtaggaaagt
1801 tggctctga ctgtggcatt gcacttgca ctgttctct ctgcagacct aggggaaaac
1861 tgcaggtgga agtgccttc tactaaggcc tctactttg ggggggatgt gccctacaga
1921 agacatagaa gatggggaaa tgccaatggg caaagagcta cttgaatac ataattctc
1981 tcaaagact cagcagaaa cctaacagc aggttaaaaa aaaagatgt ttttgggtg
2041 caagtctaac ctgtctagca tgagatctc ttgatttct gattattta ttagcttga
2101 gacaaagtga atcaactcc acttagttg accgagcata aaacagaact tgggcttct
2161 ggcagtgagg ccactgtccc atcacagatt ttaaaaata atatgattg aagtagtgt
2221 atcttcaca caa

```

Protein sequence of Homo sapiens trans-golgi network glycoprotein 48 (TGN)

```

MRFVVALVLLNVAAAGAVPLLATESVKQEEAGVRPSAGNVSTHP
SLSQRPGGSTKSHPEPQTPKDSKSSAEAQTPEDTPNKSGGEAKTLKDSSNKSAGAE
QTPKGSTSKSGSEAAQTTKDSTSKSHPELQTPKDSTGKSGAEAQTPEDSPNRSGAEPK
QKDSKSGSEAAQTTKDVPNKSGADGQTPKDGSKSGAEDQTPKDVPNKSGAEKQTPK
DGSNKSAGAEQGPIDGPKSGAEQTSKDSKPNKVPEQPSRKDHSKPISNPSDNKELP
KADTNQLADKGKLSPHAFKTESGEETDLISPPQEEVKSSSEPTEDVGPKEAEDDDTGPE
EGSPPKKEEKEKMSGSSASSENREGTLDSTGSEKDDLYPNGSGNGSAESSHFFAYLVTA
AILVAVLYIAHHNKRKIIAFVLEGRKSKVTRRPKASDYQRLDQKIFSPSPNRMVYSS
GKR

```

Figure 12. (Page 24 of 33)

AJ223352. Homo sapiens mRNA...[gi:3255996]

Homo sapiens mRNA for for histone H2B

```
1 gcggttcgcc ttcaacatgc cggaaccagc gaagtcgct cccgcgcca agaagggtc
61 gaagaaagcc gtgactaagg cgcagaagaa ggacggtaag aagcgcaagc gcagccgcaa
121 ggagagctac tccgtatacg tgtacaaggt gctgaagcag gtccaccccg acaccggcat
181 ctctctaag gccatgggaa tcatgaactc ctctgtcaac gacatctcg aacgcatcgc
241 gggtagggct tcccgctgg cgcattacaa caagcgctcg accatcacct ccaggagat
301 ccagacggcc gtgcgcctgc tctgcccgg ggagtggcc aagcacgccg tgtccgaggg
361 caccaaggcc gtcaccaagt acaccagcgc taagtaaact tgccaaggag ggactttctc
421 tggaaattcc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcgg
481 tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt
541 ccacaagcta aagctggcct ctgatctca ttcagattcc aaagagaatc atttacaagt
601 taatttctgt ctcttggc cattcctct ctttaataat catttactgt tctcaaaga
661 attgtttaca ttacccatct cctctttgc tctgagaaag agtatataag cttctgtacc
721 ccactggggg gttggggtaa tatctgtgg tctcagccc tgtacctaa taaatttga
781 tgccttttt tttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
```

Protein sequence of human histone H2B

```
MPEPAKSAPAPKKGSKKAVTKAQKKDGKKRKRKRSRKESYSVYVYK
VLKQVHPDTGISSKAMGIMNSFVNDIFERIAGEASRLAHYNKRSTITSREIQTAVRL
LPGELAKHAVSEGTKAVTKYTSK
```

Figure 12. (Page 25 of 33)**L42542. Human RLIP76 prot...[gi:974142]****Human RLIP76 protein mRNA, complete cds**

```

1 agtctggttt aactggttgg aacgactaaa gcacgtggc gcaaggaaag ctctcaact
61 cgggagctga ggcgcaggct ggccagagcg tggagaggaa agccctttcc atcctcaagg
121 ccgttgacag agatgcccg cagccacctt cgccagcacc acaccggggt gtaatggata
181 ggtaacagag aagacctcgt ccttccttag tcagggcac agcatgactg agtgcttct
241 gccccccacc agcagcccca gtgaacaccg cagggtggag catggcagcg ggcttaccg
301 gacccccagc tctgaagaga tcagccctac taagtttct ggattgtacc gcactggcga
361 gccctcacct cccatgaca tcttcatga gcctctgat gtagtgtctg atgatgagaa
421 agatcatggg aagaaaaaag ggaatttaa gaaaaaggaa aagaggactg aaggctatgc
481 agcctttcag gaagatagct ctggagatga ggcagaaagt ccttctaaaa tgaagaggtc
541 caagggaatc catgttttca agaagcccag cttttctaaa aagaaggaaa aggatttaa
601 aataaaagag aaacccaaag aagaaaagca taaagaagaa aagcacaag aagaaaaaca
661 taaagagaag aagtcaaaag actgacagc agctgatgtt gtaaacagt ggaaggaaaa
721 gaagaaaaag aaaaagccaa ttcaggagcc agaggtcct cagattgatg ttccaaatct
781 caaacccatt ttggaattc ctttggtga tgcagtagag aggaccatga tgtatgatg
841 cattcggtc cagccgtt tccgtgaatg tatagattac gtagagaagt atggcatgaa
901 gtgtgaaggc atctacagag tatcaggaat taaatcaaag gtggatgagc taaaagcagc
961 ctatgaccgg gaggagtcta caaacttga agactatgag cctaacactg tagccagttt
1021 gctgaagcag tatttgcgag accttcaga gaatttgctt accaaagagc ttatgccag
1081 atttgaagag gctgtggga ggaccacgga gactgagaaa gtgcaggaat tccagcggtt
1141 actcaaagaa ctgccagaat gtaactatct tctgatttct tggctcattg tgcacatgga
1201 ccatgtcatt gcaaggaac tggaaacaaa aatgaatata cagaacattt ctatagtct
1261 cagcccaact gtgcagatca gcaatcgagt cctgtatgtg tttttcacac atgtgcaaga
1321 actctttgga aatgtgttac taaagcaagt gatgaaacct ctgcgatggt ctaacatggc
1381 cacgatgccc acgtgccag agaccagggc gggcatcaag gaggagatca ggagacagga
1441 gtttctttt aattgtttac atcgagatct gcagggtggg ataaaggatt tgtctaaaga
1501 agaaagatta tgggaagtac aaagaatttt gacagccctc aaaagaaaac tgagagaagc
1561 taaaagacag gagtgtgaaa ccaagattgc acaagagata gccagtcttt caaaagagga
1621 tgtttccaaa gaagagatga atgaaaatga agaagtata aatattctcc ttgctcagga
1681 gaatgagatc ctgactgaac aggaggagct cctggccatg gaggagtctc tgcgccggca
1741 gattgcctca gaaaaagaag agattgaacg cctcagagct gagattgctg aaattcagag
1801 tcgccagcag cacggccgaa gtgagactga ggagtactcc tccgagagcg agagcgagag
1861 tgaggatgag gaggagctgc agatcattct ggaagactta cagagacaga acgaagagct
1921 ggaataaag aacaatcatt tgaatcaagc aattcatgag gaggcgagg ccatcatcga
1981 gctgcgcgtg cagctgcggc tgcctcagat gcagcgagcc aaggccgagc agcaggcgca
2041 ggaggacgag gaggctgagt ggcgcggggg tgcgtccag ccgccagag acggcgctct
2101 tgagccaaaa gcagctaaag agcagccaaa ggcaggcaag gagccggcaa agccatcgcc
2161 cagcagggat aggaaggaga cgtccatctg agcagcctgc gtggccgtct ggagtccgtg
2221 agactgaaag gaccgtgca tcttactgta accggggggc caggccggct ctctcgctgt
2281 acattctgta aaggtgtctt ctctctcag actctctc tgcacacgt ctgactcctt
2341 cacgtcaggc tcaggttcca tgggaggacg aagcagtggg cgattgtgg gctttaggga
2401 cagatgagtt ttccagatag tgcagctta ttgaagatt aatttcttt gtttaactaa
2461 aataactatt ttaaccttg agtggcttct ttttaacca aaaaccgtct tctttgctt
2521 tttatcaca gcagaatcag gatctcttc taticcaagg ggggaaccac accaggctag
2581 cgtgcgcct gctgtggccg ccgcgagcca cgccctctgg gatctctggt accgtcactc
2641 ttgctgtgc ctccacacc ttctcggtgc agatccctat gggggagctg cctcacgttc
2701 tctgactggt cagagcagcg cctggtggtt gttccctggc ccactctct ctctctctt
2761 gcagtctaa accacagtct ataagcccga gtcaccagga cggcctgtct ggccacagac
2821 aggggctgcc tgtggagcct gccacccggc ccccgagct gcagtccagc ggggaggagg

```

Figure 12. (Page 26 of 33)

2881 ctgcccgttc ctgccagttc ctactgctg ggaccagcaa aggccttctc actgggttgg
2941 tcaaaggtag tcacctggc ctggtgcatc cacagaggat gttgtcaaa ccagaaatct
3001 tttaaagcac tgaccttct taaaaacaga atgactccga ttgcttgctt gggctagaat
3061 gtacacgtct ccttgctga ataagccata tatatgctt taaacaaaag ttgaaatta
3121 tccatatcat ctactgaac ctactggtg actcccaatt gacaagattg agcaatagaa
3181 aaaaattcct ttctttgaa tgaatgctg gattcacccc accccatttt ctgtttctg
3241 gtccatccga tgagacggat gctctgatc tctgaggctt ctgggaggct gggccctgga
3301 ggcaacgtgc tgcaggcgca ctctgtcaga gtgaacagca ccgcgagaca ggccaggctc
3361 gtggctcga agacaaacc cacacacact caaggggtcg aaaacaaacc ccacacgagg
3421 gctctcacct ccttctcta gtagtattt atttcagca cctgtttgat gcagtttta
3481 atcctctacc tattgcactg ttgtgactcg ttggccatta ttgattttg gtacgaaaaa
3541 aagctttgtt atagaaatca gcatactatt ttttaaatc tggagagaag atattctggt
3601 gactgaaagt alggtcgggt gtcagatata aatgtgcaa tgcctcttg ctgtcctgtc
3661 ggtctcagta cgttcacatt atagctgctg gcaatatca aggttcctt ttgtttgtg
3721 taaactctaa ttctatcaa ggtgtcatg attttaaaa ttagtatttc attacaaatg
3781 tctcagcatt ggtaactaa ttgtggcag gaccattatt gatcaagcaa ataaattcaa
3841 cagccatttg gaaaaaag

Protein sequence of Human RLIP76

MTECFLPPTSSPSEHRRVEHGSGLTRTPSSEEISPTKFPGLYRT
GEPSPPHDILHEPPDVSDDEKDHGKKKGKFKKKEKRTEGYAAFQEDSSGDEAESPSK
MKRSKGIVFKKPSFSKKKEKDFKIKEKPKEEKHKKEKHKEEKHKEKSSKDLTAADV
KQWKEKKKKKKPIQEPEVPQIDVPLKPIFGIPLADAVERTMMYDGIRLPVAVFRECID
YVEKYGMKCEGIYRVSGIKSKVDELKAAYDREESTNLEDYEPNTVASLLKQYLRDLPE
NLLTKELMPRFEEACGRTTETEKVQEFQRLLKELPECNYLLISWLIVHMDHVIKELE
TKMNIQNISIVLSPTVQISNRVLYVFFTHVQELFGNVVLKQVMKPLRWSNMATMPTLP
ETQAGIKEEIRRQEFLLNCLHRDLQGGIKDLSKEERLWEVQRILTALKRKLREAKRQE
CETKIAQEIASLSKEDVSKEEMNENEEVINILLAQENEILTEQEELLAMEQLRRQIA
SEKEEIERLRAEIAEIQSRQQHGRSETEEYSSSESESESEDEEELQIILEDLQRQNEEL
EIKNNHLNQAIHEERAEIILRVQLRLLQMQRAKAEQQAQEDDEEPEWRGGAVQPPRDG
VLEPKAAKEQPKAGKEPAKPSRDRKETS

Figure 12. (Page 27 of 33)

W26677. 11f7 Human retina...[gi:1305788]

TNNNNNTTNNNNNNNTTNNCCTTGCTCAGCATTGGNTNTGATGTGCTGGTGGAGAACCACG
AAGAATGNATTGCTGAGGGGAGACCTGGTCCAGGGTCTTCTCCCCTGTAATCCAGGGCCA
CACTGATGAGNTCTGGGGGNTCTGCACACACCCCTCCCAGAACCGNTTCCTCACCTGCGG
CCACGACCGGNAGTTCTGCCTGTGGGATGGGGAGAGCCATGCACTGGCCTGGAGCATCGA
CCTCAAGGAGACTGGTCTCTGTGCTGACTTCCACCCGAGTGGGGCAGTTGTGGCCGNAGG
ACTGAACACGGGGAGGTGGTTGGTTTTGGNCACAGAGACCAGAGAGATCGTGTCTGATGT
CATTGATGGCAATNAGCAGCTCTCAGTGGTCCGGTACAGNCCAGATGGGTTGGTCCTGGC
CCAATTGGTTCCCATNACAACNTNATNTTCAATCTTTNGNGGTTTCCAGGGGATGGTG
CCCAATTCCAGNCCNTTTTGGGCCNTTTGTNTTTGGGTCAACNCCCAGNTTCAACCACTC
AATNTTGGAGTAGGTTCAANNNTTNGNNTTACCAGTTGNNNTTNTCCAANNNNNNNNNNNN
NNTNTNNNNNTNNTTNTTCTTTTNCNTNANNCNNNNNNNNNNNNCANNNTCTNCNTNTTNTC
AANCCNNNTNNNNNNNCNNNCNNNNNCNTNTNCTNCTNNNNNCNNTNNNNCTNNTNNN
CNNNNCTNNNNNTNNNCNNNNNNNN

Protein sequence of Human retina cDNA

No Protein sequence available from GenBank

Figure 12. (Page 28 of 33)**X51804. Human PMI gene fo...[gi:35534]****Human PMI gene for a putative receptor protein**

```

1 ggcccccccc cccctagaa atgctgaac caggacggct cctggagtcc tcgcgccctc
61 gcagaaggac tacgggcccc ggcgaccccg ggggcggggc ttccggcgcg ctgcctgtg
121 ggcacggtag ttccgccggg tctggcttcc gcctgccgag cggccccgga ccgcaggccg
181 gactacactt cccgtcggcc cgcctgctct cccgatgccg ccttggcgcg agacgttggc
241 aagcagagtg tctccaagat ggccgcttgg ggaaggaggc gtcttgccc gggcagcagt
301 ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtcatgag
361 atctacaatg gggagaatgc ccaagaccag tttagtacg agctggagca ggcctggaa
421 gccagtaca agtacattgt gattagccc actcgattg gcgacgagac agcccgtgg
481 atcaccgtgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctctc
541 acccgttgg cgctgccctt agattattcc cactacattt ccctgccgcg tgggtgctg
601 agctggcct gctgcacct ctatgggac tcctggcagt ttgaccttg ctgaagtac
661 caagtggagt acgacgccta taaactgtcg cgcctgcctc tgcacacact cacctctcc
721 acccgggtgg tgctgggccg gaaggacgac ctgcacagaa agagactgca caacacgata
781 gcactggccg ccctgggtga ctgtgtaaag aagatttacg aactctatgc cgtatgatt
841 cagtagaaca gggagcgaag caaaaccacc cggcccacaa gagacaacag agtattcaga
901 tcgccacact ctgtgaggca gcagagcctg ggcagggtgt tggcttagta ttgttatt
961 ttaaaaaata acagatcacg ggtgtacca gggttttca gtcattaca ctaagatgtg
1021 gatttcata acccaagagg ggggtctgag gctgtggaag tccgactggg cagtggaatg
1081 ctgatggagg cagacgctgc cgaggggggtg tggacgtgct ttgggggagg tcttaagtc
1141 tattgtttaa ctgtaccatc cagagccac cagaagctat tgatcattaa aattatgaga
1201 atttcaactc c

```

Protein sequence of Human PMI

```

MAAWGRRRLGPGSSGGSARERVSLSATDCYIVHEIYNGENAQDQ
FEYELEQALEAQYKYIVIEPTRIGDETARWITVGNCLHKTAVLAGTACLFPLALPLD
YSHYISLPAGVLSLACCTLYGISWQFDPCKYQVEYDAYKLSRLPLHTLSSTPVVLV
RKDDLHRKRLHNTIALAALVYCVKKIYELYAV

```


Figure 12. (Page 29 of 33)**M24069. Human DNA-binding...[gi:181483]****Human DNA-binding protein A (dbpA) gene, 3' end**

1 gaattcgggc gggggagccc aaggagcgag cgcgccagac gaagctcgag ccgcctccgc
 61 cagcgcgacc ccacctcggc cgccggcctg cgccgcgaga tccgccccgg cctccccgag
 121 agcgagcccc ggccgcccgc accaccagcc gcgctaaccg ccgaccaacc gccaccgagg
 181 cgctgagcg agagcagagg aggaggaggc atgagtgagg cgggcgaggc caccaccacc
 241 accaccacca cctccccga ggctccgacg gaggcggccg ccgcggctcc ccaggacccc
 301 gcgccaaga gcccgggtgg cagcgggtgc cccaggccg cgccccggc gcccgccgcc
 361 cagctcgag gaaaccccg tgggacgcg gccctgcag ccacgggcac cgcggccgcc
 421 gcctcttag ccgccggcg cggcagcgaa gacgcggaga aaaaagtct cgcaccaaa
 481 gtcctggca ctgtcaaatg gttaacgtc agaaatggat atggattat aaatcgaaat
 541 gacacaaaag aagatgtatt tgtacatcag actgccatca agaagaataa cccacggaaa
 601 tatctgcga gtgtaggaga tggagaaact gtagagttg atgtggtga aggagagaag
 661 ggtgcagaag ctgcaatgt gactggccc gatggagttc ctgtggaagg gagtcttac
 721 gctgcagatc ggcgcggtta cagacgtggc tactatgga ggcgcgltg cctccccgg
 781 aattacgtg gggaggagga ggaggaaggg agcggcagca gtgaaggatt tgacccccct
 841 gccactgata ggcagttctc tggggcccg aatcagctgc gccgccccca gtatcgccct
 901 cagtaccggc agcggcggtt cccgccttac cagtggtgac agaccttga ccgtcgctca
 961 cgggtcttac ccatcccaa cagaatacag gctggtgaga ttgagagat gaaggatgga
 1021 gtccagagg gagcacaact tcagggaccg gtcatcgaa atccaacta ccgccaagg
 1081 tacctagca ggggacctc tcgccacga cctgccccag cagttggaga ggctgaagat
 1141 aaagaaaatc agcaagccac cagtgttcca aaccagccgt ctgtcgccg tggataccg
 1201 cgtccctaca attaccggc tcgcccgccg tctcctaac gtcctctac aagatggca
 1261 agaggccaag gcagggaag caccaactga gaacctgct caccacccc agcagagcag
 1321 tgtgagtaac accaggctcc tcaggcacct tcacctcgg caggtggacc taaagaatta
 1381 gatgaccatt cagaaataaa gcaaaaagca ggccacatac ctaaccaac accaaagaaa
 1441 catccaagca ataaagtga agactaacca agattggac attggaatgt ttactgtat
 1501 tcttaagaa acaactacaa aaagaaaatg tcaacaaatt ttccagcaa gctgagaacc
 1561 tggaattc

Protein Sequence of Human DNA-binding protein A (dbpA)

EFGRGSPRSEARRSSSLRQRDPTSAAGLRREIRPGLPESEPR
 PPRPPAALTADQPPPRRLSESRGGGMSEAGEATTTTTTLPQAPTEAAAAAPQDPAP
 KSPVSGSAPQAAAPAPAAHVAGNPGDAAPAATGTAAAASLAAAAGSEDAEKKVLATK
 VLGTWKWFNVRNGYGFINRNDTKEDVFVHQTAIKKNNPRKYLRVSGDGETVEFDVVEG
 EKGAEEANVTGPDGVPVEGSRYAADRRRYRRGYGRRRGPPRNYAGEEEEEEGSGSSEG
 FDPATDRQFSGARNQLRRPQYRQYRQRRFPYHVGQTFDRRSRVLPHPNRIQAGEI
 GEMKDGVPGEAQLQGPVHRNPTYRPRYRSRGPPRPRPAPAVGEAEDKENQQATSGPNQ
 PSVRRGYRRPYNYRRPPSS

Figure 12. (Page 30 of 33)

NM_002218. Homo sapiens inte...[gi:4504784]:

Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITI4)

DNA sequence:

```

1  gtgagaagcc tcttggcaga cactggagcc acgatgaagc cccaaggcc tgcctgacc
61  tgcagcaaag ttctgtctct gctttactg ctggccatcc accagaccac tactgccgaa
121  aagaatggca tcgacatcta cagcctcacc gtggactcca ggggtctatc ccgatttgcc
181  cacacggctg tcaccagccg agtggtaaat agggccaata cggtagagga ggccaccttc
241  cagatggagc tgcccaagaa agccttcac accaactct ccatgaacat cgatggcatg
301  acctaccagc gcatcatcaa ggagaaggct gaagcccagg cacagtacag cgagcagtg
361  gccaaaggaa agaagcgtgg cctgtcaag gccaccggga gaaacatgga gcagtccag
421  gtgtcggta gtgtggctcc caatgccaag atcaccttg agtggctta tgaggagctg
481  ctaagcggc gtttgggggt gtacgagctg ctgtgaaag tgcggcccca gcagctggc
541  aagcacctgc agatggacat tcacatcttc gagccccagg gcatcagctt tctggagaca
601  gagagcacct tcagaccaa ccagctggta gacgcccata ccacttgga gaataagacc
661  aaggctcaca tccgggtcaa gccaacactt tccagcagc aaaagtcccc agagcagcaa
721  gaaacagctc tggacggcaa cctcattatc cgctatgatc tggaccgggc catctccggg
781  ggctccattc agatcgagaa cggctacttt gtacactact ttgccccga gggcctaacc
841  acaatgcca agaattgtgt cttgtcatt gacaagagcg gctccatgag tggcaggaaa
901  atccagcaga cccgggaagc ctaatacaag atcctggatg acctagccc cagagaccag
961  ttcaacctca tcgtcttcag tacagaagca actcagtga ggccatcact ggtgccagcc
1021  tcagccgaga acgtgaacaa ggccaggagc ttgtctcggc gcatccaggc cctgggaggg
1081  accaacaatc atgatgaat gctgatggct gtgcagttgc tggacagcag caaccaggag
1141  gagcggctgc ccgaaggag gtgtctactc atcatctgc tcaccgatg cgacccact
1201  gtgggggaga ctaacccag gagcatccag aataacgtgc gggaagctgt aagtggccgg
1261  tacagcctct tctgctggg ctcgggttc gacgtcagct atgccttct ggagaagctg
1321  gactggaca atggcgccct ggccggcgc atccatgagg actcagactc tgcctgcag
1381  ctccaggact taccagga agtggccaac ccactgtga cagcagtgac ctccagtag
1441  ccaagcaatg ccgtggagga ggtcactcag acaacttcc ggctcctct caagggtca
1501  gagatgttgg tggctgggaa gctccaggac cgggggctg atgtgtcac agccacagtc
1561  agtgggaagc tgctacaca gaacatcact ttccaaacgg agtccagtgt ggcagagcag
1621  gagcgaggat tccagagccc caagtatac ttccaaact tcattggag gctctgggca
1681  tacctgacta tccagcagct gctggagcaa actgtctccg catccgacgc tgatcagcag
1741  gccctccgga accaagcgt gaattatca ctgctcaca gcttgcac gccttcaca
1801  tctatggtag tcacaaacc cgtatgacaa gagcagctc aagtgtctga gaagccatg
1861  gaaggcgaaa gtagaaacag gaatgtccac tcaggttcca ctttctcaa atattatc
1921  caggagcaga aaataccaaa accagaggct tcttttctc caagaagagg atggaataga
1981  caagctggag ctgtgtgctc ccggtgaat ttccagctg ggggtctcag ctccaggcaa
2041  cttggactcc caggacctcc tgatgtctct gacctgtg cttaccaccc ctccgccgt
2101  ctggccatct tgcctgttc agcaccacca gccacctcaa atcctgatcc agctgtgtct
2161  cgtgtcatga atatgaaaat cgaagaaaca accatgacaa cccaaacccc agccccata
2221  caggctccct ctgcatctct gccactgcct gggcagagtg tggagcggct ctgtgtggac
2281  ccagacacc gccaggggac agtgaacctg ctctcagacc ctgagcaagg ggttgaggtg
2341  actggccagt atgagagggg gaaggctggg ttctcatgga tcgaagtgc cttcaagaac
2401  cccctggtat ggttcacgc atcccctgaa cagtgtgtg tgactcggaa ccgaagaagc
2461  tctgcgtaca agtgaagga gacgtattc tcagtgtgc ccggcctgaa gatgacctg
2521  gacaagacgg gtctctgtct gctcagtgac ccagacaaag tgacctcgg cctgtgttc
2581  tggatggcc gtggggagg gctccggctc cttctgctg acactgacc cttctcagc
2641  caggttgag ggaccttg ccagttttac caggaggtgc tctggggatc tccagcagca
2701  tcagatgacg gcagacgcac gctgagggtt cagggcaatg accactctgc caccagagag

```

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2761 cgcaggctgg attaccagga ggggcccccg ggagtgagga ttctctgctg gtctgtggag
2821 ctgtagtct gatggaagga gctgtgcca cctgtacac ttggctccc cctgcaactg
2881 cagggccgct tctggggcct ggaccacat ggggaggaag agtcccactc attacaaata
2941 aagaaagggtg gtgtgagcct ggg

Protein sequence for Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITI4):

MKPPRPVRTCSKVLVLLSLLAIHQTTTAEKNGIDIYSLTVDSRVSSRFAHTVVTSRVVRANTVQEATFQMELPKKAFIT
NFSMNIDGMTYPGIIKEAEQAQYSAAVAKGKNAGLVKATGRNMEQFQVSVSVAPNAKITFELVYEELLKRRLGVYE
LLLKVRPQQLVKHLQMDIHIFEPQGISFLETSTFMTNQLVDALTTWQNKTKAHIRFKPTLSQQQKSPEQQETVLDGNL
IIRYDVEDRAISGGSIQIENG YFVHYFAPEGLTTPKNNVFVIDKSGSMSGRKIQQTREALIKILDDLSPRDQFNLIVFSTE
ATQWRPSLVPASAENVNKARSFAAGIQALGGTNINDAMLMVQLLDSSNQEERLPEGSVSLIILLTDGDPTVGETNPR
SIQNNVREAVSGRYSLFCLGFGFDVSYAFLEKLALDNGGLARRIHEDSDSALQLQDFYQEVANPLLTAVTFEYPSNAV
EEVTQNNFRLLFKGSEMVVAGKLQDRGPDVLTATVSGKLPTQNITFQTESSVAEQEAEFQSPKYIFHNFMERLWAYL
TIQQLLEQTVSASDADQQALRNQALNLSLAYSFVTPLTSMVVTKPDDQEQSQVAEKPMEGESRNRNVHSGSTFFKYY
LQGA KIPKEASFSPRRGWN RQAGAAGSRMNFRPGVLSSRQLGLPGPPDVPDHAAYHPFRR LAILPASAPPATSNP
DPAVSRVMNMKIEETMTTQTPAPIQAPSAILPLPGQSVERLCVDPRHRQGPNLLSDPEQQGVEVTGQYEREKAGFS
WIEVTFKNPLVWVHASPEHV VTRNRRSSAYKWETLFSVMPGLKMTMDKTGLLLSDPKVTIGLLFWDGRGEGLR
LLRDTDRFSSHVGGTLGQFYQEV LWGSPAASDDGRRTL RVQGNDHSATRERRLDYQEGPPGVEISCWSVEL

Figure 12. (Page 32 of 33)

NM_000584. Homo sapiens interleukin 8 (IL8), mRNA.[gi:28610153]

```

1 ctccataagg cacaaacttt cagagacagc agagcacaca agcttctagg acaagagcca
61 ggaagaaacc accggaagga accatctcac tgtgtgtaaa catgacttcc aagctggccg
121 tggctctctt ggcagccttc ctgattctg cagctctgtg tgaagggtgca gtttgccaa
181 ggagtgtctaa agaacttaga tgtcagtgc taaagacata ctccaaacct ttccacccca
241 aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaac acagaaatta
301 ttgtaaagct ttctgatgga agagagctct gtctggaccc caaggaaaac tgggtgcaga
361 ggggtgtgga gaagttttg aagagggctg agaattcata aaaaaattca ttctctgtgg
421 tatccaagaa tcagtgaaga tgccagtga acttcaagca aatctacttc aacacttcat
481 gtattgtgtg ggtctgtgt aggggtgcca gatgcaatac aagattctct gttaaatttg
541 aatttcagta aacaatgaat agttttcat tgtacatga aatatccaga acatacttat
601 atgtaaagta ttatttatt gaatclacaa aaaacaacaa ataatttta aatataagga
661 tttcctaga tattgcacgg gagaatatac aaatagcaaa attgaggcca agggccaaga
721 gaatalccga actttaattt caggaattga atgggtttgc tagaatgtga tatttgaagc
781 atcacataaa aatgatggga caataaattt tgccataaag tcaaatttag ctggaatcc
841 tggattttt tctgttaa tctgcaacct tagtctgcta gccaggatcc acaagtcctt
901 gttccactgt gccttggtt ctctttatt tctaagtga aaaagtatta gccaccatct
961 taccicacag tgatgtgtg aggacatgtg gaagcacttt aagtttttc atcataacat
1021 aaattatttt caagtgaac ttattaacct atttattatt tatgtattta tttaagcatc
1081 aaatatttgt gcaagaattt ggaataatag aagatgaatc attgattgaa tagttataaa
1141 gatgttatag taaatttatt ttattttaga tattaaatga tgtttatta gataaatttc
1201 aatcagggtt ttagatttaa acaacaaac aattgggtac ccagttaaat ttcatattca
1261 gataaacaac aaataatttt ttagtataag tacattattg ttatctgaa attttaattg
1321 aactaacaat cctagtttga tactcccagt ctgtcattg ccagctgtgt tggtagtgct
1381 gtgttgaatt acggaataat gagttagaac tattaaaaca gccaaaactc cacagtcaat
1441 attagtaatt tctgtctgt tgaacttgt ttattatga caaatagatt cttataatat
1501 tatttaaatg actgcatttt taaatacaag gctttatatt tttaacttta agatgttttt
1561 atgtgtcttc caaattttt ttactgttc tgattgtatg gaaatataaa agtaaatatg
1621 aaacatttaa aatataattt gttgtcaaag taataaaaaa aaaaaa

```

Protein sequence for Interleukin 8 precursor

```

1 mtsklavall aafllisaalc egavlprsak elrcqckty skpfhpkfik elrviesgph
61 canteiivkl sdgreldcp kenwvqrve kflkraens

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Figure 12. (Page 33 of 33)

M11725. Human C-reactive protein gene, complete cds.[gi:181067]

```

1 ttgcttccc ctctcccca agctctgaca cctgcccaca caagcaatgt tggaaaatta
61 ttacatagt ggcgcaaact cccttactgc ttggaataa aatccaggca ggaggaggta
121 gctctaaggc aagagatctg ggacttctag cccctgaact ttcagccgaa tacatctttt
181 ccaaaggagt gaaticaggc cctgtatca ctggcagcag gacgtgacca tggagaagct
241 gttgtgttc ttggtctga ccagcctctc tcatgcttt ggccagacag gtaagggcca
301 ccccaggcta tgggagagt ttgatctgag gtatgggggt ggggtctaag actgcatgaa
361 cagtctcaaa aaaaaaaaaa aaagactgta tgaacagaac agtggagcat cctcatggt
421 gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gagaaggggt cagtctgtt
481 ctcaatctta aattctatac gtaagtgagg gtagatgact gtgtgatctg agaaacctct
541 cacatttctt tgttttctg gctcacagac atgtcgagga aggcctttgt gttcccaaa
601 gagtcggata ctctctatgt atccctcaaa gcaccgttaa cgaagcctct caaagccttc
661 actgtgtgcc tccacttcta caggaactg tctcgaccc gtgggtacag tattttctcg
721 tatgccacca agagacaaga caatgagatt ctcatatttt ggtctaagga tataggatac
781 agttttacag tgggtgggtc tgaatatla ttcgagggtc ctgaagtcac agtagctcca
841 gtacacattt gtacaagctg ggagtcgcc tcagggatcg tggagttctg gtagatggg
901 aagcccaggg tgaggaagag tctgaagaag ggatacactg tgggggcaga agcaagcatc
961 atcttggggc agggagcagga ttcttctggt gggaactttg aaggaagcca gtccctggtg
1021 ggagacattg gaaatgtgaa catgtgggac ttgtgtgtgt caccagatga gattaacacc
1081 atctatcttg gcggggccct cagtctaat gtctgaact ggcgggcact gaagtatgaa
1141 gtgaaggcgc aagtgttac caaacccag ctgtggccct gaggccagct gtgggtctg
1201 aaggtaacct ccggtttttt acaccgcatg ggccccacgt ctctgtctct ggtacctccc
1261 gcttttttac actgcatggt tcccacgtct ctgtctctgg gcctttgttc ccctatatgc
1321 atgaggcctt gctccacctt cctcagcgcc tgagaatgga ggtaaagtgt ctggtctggg
1381 agctcgtaa ctatgtctgg aaatgttcca aaagaatcag aatttgaggt gttttgttt
1441 cattttatt tcaagtggga cagatcttgg agataatttc ttacctaca tagatgagaa
1501 aactaacacc cagaaaggag aaatgatgtt ataaaaaact cataaggcaa gagctgagaa
1561 ggaagcgctg atcttctatt taattcccca cccatgaccc ccagaaagca ggagcattgc
1621 ccacattcac agggctcttc agtctcagaa tcaggacact ggccagggtg ctggtttggg
1681 tccagagtgc tcatcatcat gtcatagaac tgcctggccc aggtctcctg aaatgggaag
1741 cccagcaata ccacgcagtc cctccacttt ctcaaagcac actggaaagg ccattagaat
1801 tggccagca gagcagatct gcttttttc cagagcaaaa tgaagcacta ggtataaata
1861 tgtgttact gccaagaact taaatgactg gttttgtt gctgcagtg ctcttctaat
1921 ttatggctc ttctgggaaa ctctcccct ttccacacg aacctgtgg ggctgtgaat
1981 tcttttca tcccgcatt ccaatatac ccaggccaca agagtggacg tgaaccacag
2041 ggtgtcctgt cagaggagcc catctccat ctcccagct ccctatctgg aggatagttg
2101 gatagttacg tgttctagc aggaaccaact acagtcttc caaggattga gttatggact
2161 ttgggagtga gacatcttct tctgtctgga ttccaagct gagaggacgt gaacctggga
2221 ccaccagtag ccatcttgtt tgccacatgg agagagactg taggacaga agccaaactg
2281 gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa
2341 tcagccttgt ctggaaccag atctacacct ggactgcca ggtctataag ccaataaagc
2401 cctgttttac ttgagtgagt ccaagctgtt ttctgtagt tgcttagaa gttgtgacta
2461 acttctctat gaccttgaa

```

Protein sequence for C-reactive protein

```

1 meklclflvl tslshafgqt dmsrkafvfp kesdtsyvsf kapltkplka ftvclhfyte
61 lsstrgysif syatrkdne ilifwskdig ysftvggsei lfevpevtva pvhictswes
121 asgivefwvd gkprvrslk kgytvgaeas iilgqeqlsf ggnfegsqsl vgdignvnmw
181 dfvlspdein tiylgpfsp nvlwnralky evqgevftkp qlwp

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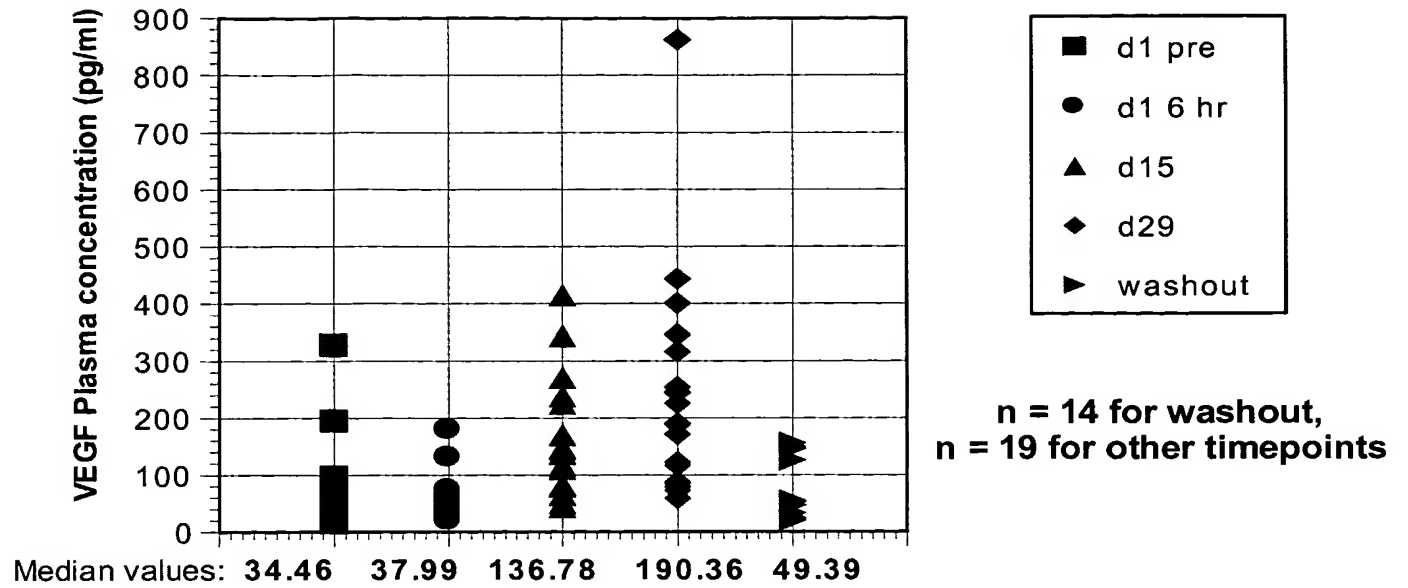
Figure 13.

Figure 14.

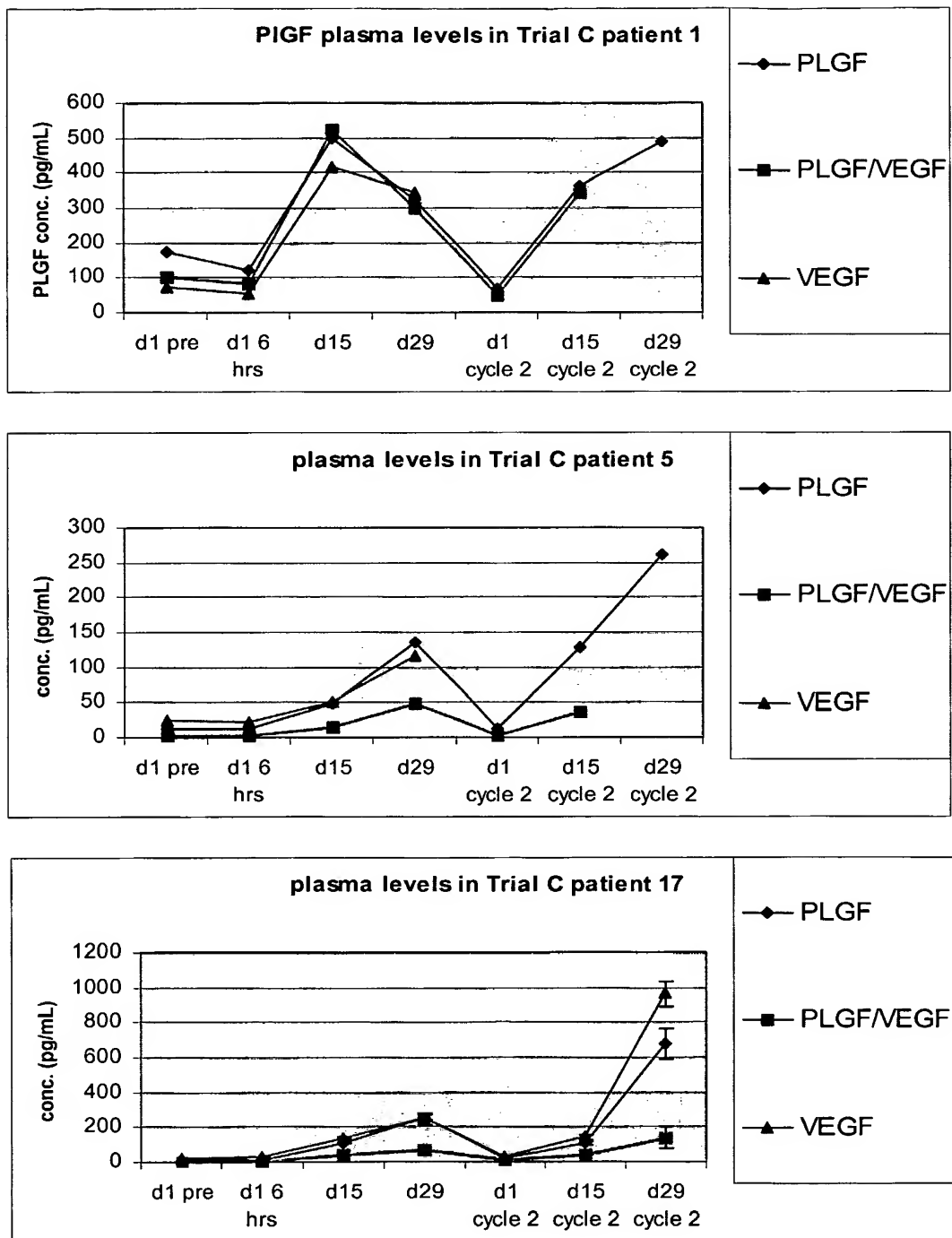


Figure 15.

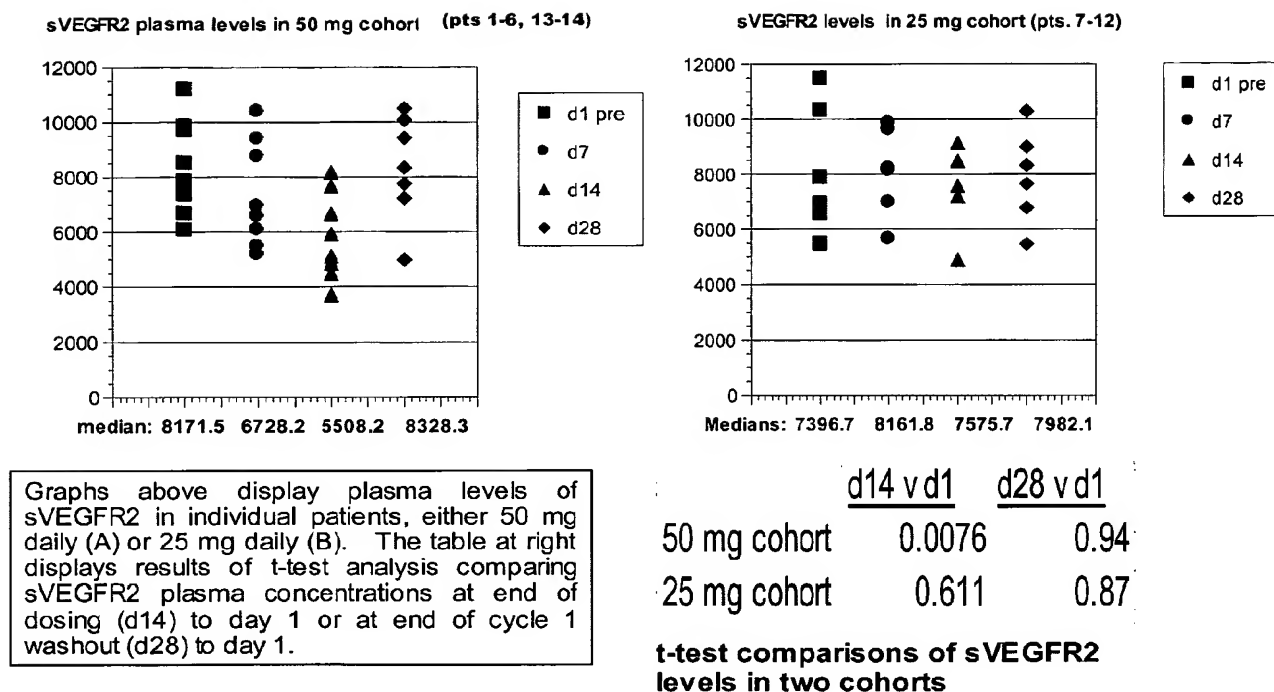
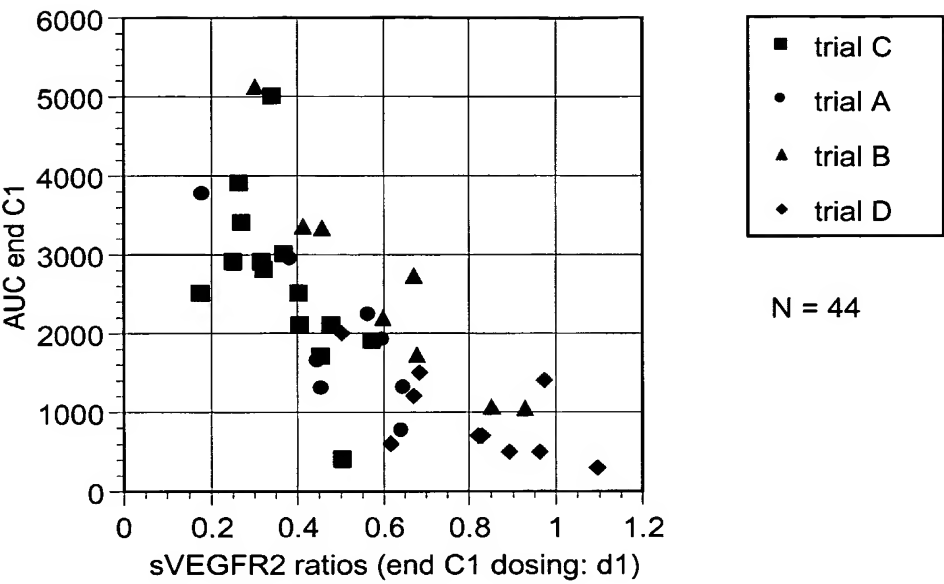
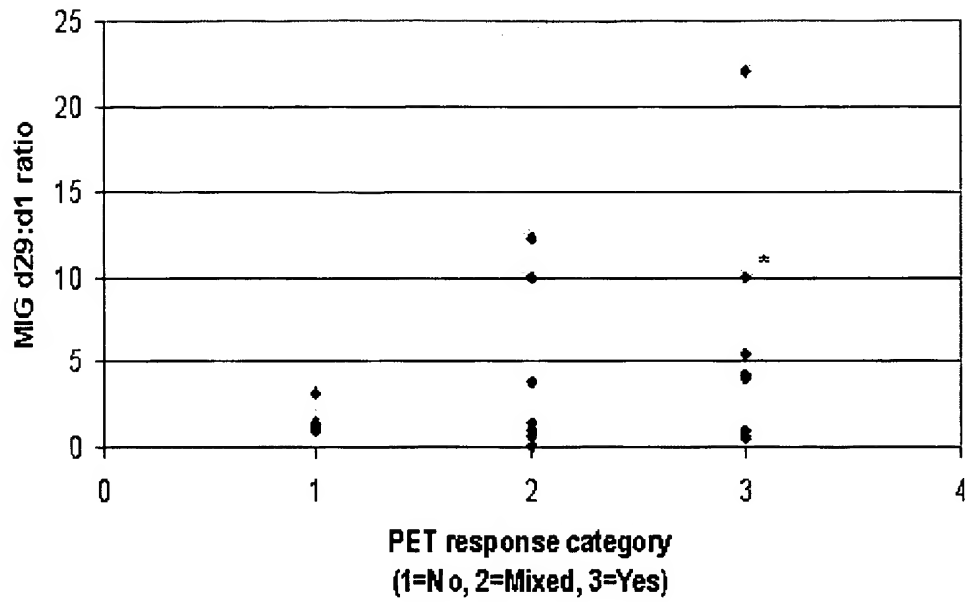


Figure 16.



R-squared = 0.5773

Figure 17.



1: n = 6. 2: n = 8. 3: n = 8

*estimated minimum ratio

Figure 18.**NP_003367 vascular endothelial growth factor [gi:19923240]**

1 mnflswvhw slallylhh akwsqaapma eggqnhhev vkfmdvyqrs ychpietlvd
61 ifqeypdeie yifkpscpl mrcggcsnde glecvptees nitmqimrik phqgqhigem
121 sflqhnkcec rpkkdrarqe npcgpserr khlfvqdpqt ckcscknths rckarqlen
181 ertcrecdkpr r

Figure 19.**P49763 Placenta growth factor [gi:17380553]**

1 mpvmrlfpcf lqllaglalp avppqqwals agngssevev vpfqevwgrs ycralerlvd
61 vvseyipseve hmfspscvsl lrtgccgde nlhcvpveta nvtmqllkir sgdrpsyvel
121 tfsqhvrcec rhspgrqspd mpgdfradap sflpprrslp mlfrmewgca ltgsqsavwp
181 sspvpeeipr mhpgrngkkq qrkplrekmk percgdavpr r

Figure 20.**P35968 Vascular endothelial growth factor receptor 2 [gi:9087218]**

1 mqsksvllava lwlcvetraa svglpsvsld lprlsiqkdi ltikanttlq itcrgqrdld
61 wlwpnnqsgs eqrvevtecs dglfckltli pkvigndtga ykcfyretld asviyvyvqd
121 yrspfiassvs dqhgvyvite nknktvvipec lgsislnvs lcarypekrf vpdgnriswd
181 skkgftipsy misyagmvfc eakindesyq simyivvvvg yriydvvlsp shgielsvge
241 klvlnctart elnvgidfnw eypsskhqhk klvnrldktq sgsemkkfls tltidgvtrs
301 dqglytcaas sglmtkknst fvrvehkpfv afgsgmeslv eatvgervri pakylgyppp
361 eikwykngip lesnhtikag hvltimevse rdtgnytvil tnpiskekqs hvvslvvyvp
421 pqigekslis pvdsyqygtt qtlctvyai ppphhihwyw qleeeacanep sqavsvtnpy
481 pceewrsved fqggnkievn knqfaliegk nktvstlvliq aanvsalykc eavnkvggrge
541 rvisfhvtrg peitlqpdmq pteqesvslw ctadrstfen ltwyklgpqp lpihvgelpt
601 pvcknldtlw klnatmfsns tndilimelk naslqdgdy vclaqrktk krhcvvrqlt
661 vlervaptit gnlenqttsi gesievscta sgnpppqimw fkdnetlved sgivlkdgnr
721 nltirrvrke deglytcqac svlgcakvea ffiiegaqek tnleiiilvg taviamffwl
781 llviilrtvk ranggelktg ylsivmdpde lpdehcerl pydaskwefp rdrklgkpl
841 grgafgqvie adafgidkta tctrvavkml kegathsehr almselkili highhlnvvn
901 llgactkpgg plmvivefck fglnstylrs krnefvpykt kgarfrqgkd yvgaipvdlk
961 rrlsitsqq ssassgfvee ksldveeee apedlykdfl tlehlicysf qvakgmefla
1021 srkcihrdla arnillsekn vvkicdfgla rdiykdpdyv rkgdarlpk wmapetifdr
1081 vytiqsdvws fgvlleifs lgaspypgvk ideefcrrlk egtrmrapdy ttpemyqtml
1141 dcwhgepsqr ptfselvehl gnllqanaqq dgkdyivlpi setlsmeeds glslptspvs
1201 cmeeeevcdp kfhydntagi sqylqnskrk srpvsvktfe dipleepevk vipddnqtds
1261 gmvaseelk tledrtklsp sfggmvpssks resvasegsn qtsqyqsyh sddtdttvys
1321 seeaellkli eigvqtgsta qilqpdsgtt lssppv

Figure 21.

Q07325 Small inducible cytokine B9 precursor (CXCL9) (Gamma interferon induced monokine) (MIG) [gi:585487]

1 mkksgvlfl giillvligv qgtpvvrkgr cscistnqgt ihlqslkdlk qfapspcek
61 ieiiatlknq vqtclnpdsa dvkelikkwe kqvsqkkkqk ngkqhkkkv lkvrksqrsr
121 qkkt

Figure 22.

NP_001556 **interferon-inducible cytokine IP-10 [gi:4504701]**

1 mnqtailicc lifltlsgiq gvplsrtrvc tcisisnqpvr nprlekley ipasqfcprv
61 eiatmkkkg ekrcnpsk aiknllkavs kemskrsp

Figure 23.

O14625 Interferon-inducible T-cell alpha chemoattractant (I-TAC)[gi:7674360]

1 msvkgmaial avilcatvvq gfpmfkggrc lcigpgvkav kvadiekasi mypsnncdki
61 eviitlkenk gqrclnpksk qarliikkve rknf

Figure 24. (Page 1 of 46)**M33308. Human vinculin mR...[gi:340236]****Human vinculin mRNA, complete cds**

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1 gaattccact tctctgtcgc ccgcgggtcg ccgccccgct cgcgcgcgcg atgccagtgt
61 ttcatcgcg cagcatcgag agcatcctgg agccgggtggc acagcagatc tcccacctgg
121 tgataatgca cgaggagggc gaggtggacg gcaaagccat tcttgacctc accgcgccccg
181 tggccgccgt gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa
241 ccactgagga tcagattttg aagagagata tggcaccagc atttattaag gttgagaatg
301 cttgcaccaa gcttgccag gcagctcaga tgcctcagtc agacccttac tcagtgcctg
361 ctcgagatta tctaattgat gggtaagggt gcacctcttc tggaacatca gacctgctcc
421 ttaccttca tgaggctgag gtccgtaaaa ttattagagt ttgcaaagga attttggaat
481 atcttacagt ggcagagggtg gtggagacta tggaagattt ggtcacttac acaaagaatc
541 ttgggccagg aatgactaag atggccaaga tgattgacga gagacagcag gagctcactc
601 accaggagca ccgagtgatg ttgtgaact cgatgaacac cgtgaaagag ttgctgccag
661 ttctcatttc agctatgaag atttttgtaa caactaaaaa ctcaaaaaac caaggcatag
721 aggaagcttt aaaaaatcgc aattttactg tagaaaaaat gagtgtgtaa attaatgaga
781 taattcgtgt gttacaactc acctcttggg atgaagatgc ctgggccagc aaggacactg
841 aagccatgaa gagagcattg gcctccatag actccaaact gaaccaggcc aaagggtggc
901 tccgtgacct tagtgctccc ccagggggatg ctggtgagca ggccatcaga cagatcttag
961 atgaagctgg aaaagttggt gaactctgtg caggcaaaga acgcaggagc attctgggaa
1021 cttgcaaaat gctagggcag atgactgacg aagtggctga cctccgtgcc agaggacaag
1081 gatcctcacc ggtggccatg cagaaagctc agcaggtatc tcagggtctg gatgtgctca
1141 cagcaaaagt ggaaaatgca gctcgcaagc tggaagccat gaccaactca aagcagagca
1201 ttgcaaagaa gatcgatgct gtcagaact ggctgcaga tccaaatggt ggaccggaag
1261 gagaagagca gattcgaggt gcttggctg aagctcggaa aatagcagaa ttatgtgatg
1321 atcctaaaga aagagatgac attctacgtt cccttgggga aatatctgct ctgacttcta
1381 aatagcaga tctacgaaga caggggaaaag gagattctcc agaggctcga gccttggcca
1441 aacagggtggc cacggccctg cagaacctgc agacaaaac caaccgggct gtggccaaca
1501 gcagaccggc caaagcagct gtacaccttg agggcaagat tgagcaagca cagcggtgga
1561 ttgataatcc cacagtggat gaccgtggag tcggtcaggc tgccatccgg gggcttgttg
1621 ccgaagggca tcgtctggct aatgttatga tggggcctta tcggcaagat ctctcgcca
1681 agtgtgaccg agtggaccag ctgacagccc agctggctga cctggctgcc agagggggaag
1741 gggagagtcc tcaggcacga gcacttgcac ctacagctca agactcctta aaggatctaa
1801 aagctcggat gcaggaggcc atgactcagg aagtgtcaga tgtttcagc gataccacaa
1861 ctcccatcaa gctgttggca gtggcagcca cggcgcctcc tgatgcgcct aacagggaag
1921 aggtatttga tgagagggca gctaactttg aaaaccattc aggaagctt ggtgctacgg
1981 ccgagaaggc ggctgcggtt ggtactgcta ataatcaac agtggaaggc attcaggcct
2041 cagtgaagac ggcccagaaa ctacaccccc aggtggtctc ggctgctcgt atcttactta
2101 ggaaccttgg aaatcaagct gcttatgaac attttgagac catgaagaac cagtggatcg
2161 ataattgtga aaaaatgaca gggctggttg acgaagccat tgataccaaa tctctgttgg
2221 atgcttcaga agaagcaatt aaaaaagacc tggacaagtg caaggtagct atggccaaca
2281 ttacgcctca gatgtgtggt gctggggcaa ccagtattgc tcgtcgggcc aaccggatcc
2341 tgctggtggc taagagggag gtggagaatt ccgaggatcc caagtccgt gaggtgtgta
2401 aagctgcctc tgatgaattg agcaaaacca tctcccaat ggtgatggat gcaaaagctg
2461 ttgctggaaa catttccgac cctggactgc aaaagagctt cctggactca ggatacggga
2521 tcctgggagc tgtggccaag gtcagagaag cttccaacc tcaggagcct gacttcccgc
2581 gcctccacc agaccttgaa caactccgac taacagatga gcttgctcct cccaaaccac
2641 ctctgcctga aggtgaggtc cctccaccta ggctccacc accagaggaa aaggatgaag

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Figure 24. (Page 2 of 46)

2701 agttccctga gcagaaggcc ggggaggtga ttaaccagcc aatgatgatg gctgccagac
2761 agctccatga tgaagctcgc aaatggtcca gcaagggcaa tgacatcatt gcagcagcca
2821 agcgcatggc tctgctgatg gctgagatgt ctcggctggt aagagggggc agtggtacca
2881 agcgggcact cttcagtggt gccaaggaca tcgccaaggc ctcagatgag gtgactcggg
2941 tggccaagga ggttgccaag cagtgcacag ataaacggat tagaaccaac ctcttacagg
3001 tatgtgagcg aatcccaacc ataagcacc agctcaaaat cctgtccaca gtgaaggcca
3061 ccatgctggg ccggaccaac atcagtgatg aggagtctga gcaggccaca gagatgctgg
3121 ttacaatgc ccagaacctc atcagtgctg tgaaggagac tgtgcgggaa gctgaagctg
3181 ctcaatcaa aattcgaaca gatgctggat ttactctgcg ctgggttaga aagactccct
3241 ggtaccagta ggcacctggc tgagcctggc tggcacagaa acctctacta aaaagaagga
3301 aaatgatctg agtcccagga gctgccaga gttgctgga gctgaaaaat cacatcctgg
3361 cctggcacat cagaagga tgggggcctc ttcaaatag aagacattta tactctttt
3421 tcatggacac ttgaaatgt gtttctgtat aaagcctgta ttctcaaaca cagttacact
3481 tgtgcacct ctatcccaat aggcagactg ggtttctagc ccatggactt cacataagct
3541 cagaatccaa gtgaacacta gccagacact ctgctctgcc ctgttccct aggggacact
3601 tccctctgtt tctcttccct tggtcccat tcactctcc agaatccaa gacccagggc
3661 ccaggcaaat cagtactaa gaagaaaatt gctgtgcctc ccaaaattgt ttgagctt
3721 ccatgttctg gccaacata cttctctcc ctgggctgtg ctacctgggt cttttcaga
3781 agtgagcttt gctgtacag gggaagggtg cctctgtgga gcccagcat atgggggcct
3841 ggattcattt cctgcccctc ctcagtttaa tcttctagt tcccacaat ataaaactgt
3901 acttactgt caggaagaaa tcacagaatc atatgattct gctttacca tgcccctgag
3961 caatgtctgt gtagggaaa ctcccgtcc catatctgc ctcagcccgc caaggtagcc
4021 atccatgaa cacactgtgt cctggtgctc tctgacctg gaagggcaga gtagccaggg
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4381 gtttaattgc aaggcagccc tgtctgaagg acacttctg cctaaggag agtggtattt
4441 gcagactaga attctagtgc tctgaagat gaatcaatgg gaaatactac tctgtaatt
4501 cctacctccc tgcaaccaac tacaaccaag ctctctgcat ctactccaa gtatggggtt
4561 caagagagta atgggtttca ttttctat caccacagta agttctact aggc aaaatg
4621 agagggcagt gtttctttt tggacttat tactgctaag tattcccag cacatgaaac
4681 cttattttt ccaagccag aaccagatga gtaaaggagt aagaacctg cctgaacatc
4741 ctctctccc acccatcgt gtgtgttagt tccaacatc gaatgtgtac aacttaagt
4801 ggtccttac actcaggctt tctatttc cttaaaatg aggatgatta tttcaaggc
4861 cctcagcata ttgtatagt tcttgctg atataaatgc aatattaatg ctttaaaatg
4921 atgaatctat gccaaagatc actgtgtgt ttactaaaga aagattact agaggaaata
4981 agaaaaatca tgttgctct cccggtctt ccagtgttt gagacactgg ttacacttt
5041 atgccggatg tgttttctc caatatcagt gctcgagaca cagtgaagca aattaaaaa
5101 aa

Figure 24. (Page 3 of 46)**Protein Sequence of Human vinculin:**

MPVFHTRTIESILEPVAQQISHLVIMHEEGEVDGKAIPDLTAPV
AAVQAAVSNLVRVGKETVQTTEDQILKRDMPPAFIKVENACTKL VQAAQMLQSDPYSV
PARDYLDGSRGILSGTSDLLLT FDEAEVRKIIRVCKGILEYLTVAEVVETMEDLVTY
TKNLGPGMTKMAKMIDERQQELTHQEHRVMLVNSMNTVKELLPVLISAMKIFVTTKNS
KNQGIEEALKNRNFTVEKMSAEINEIIRVLQLTSWDEDAWASKDTEAMKRALASIDSK
LNQAKGWLRDPSASPGDAGEQAIRQILDEAGKVGELCAGKERREILGTCKMLGQMTDQ
VADLRARGQGSSPVAMQKAQQVSQGLDVLTA KVENAARKLEAMTNSKQSIKKIDAAQ
NWLADPNGGPEGEEQIRGALAEARKIAELCDDPKERDDILRSIGEISALTSKLADLRR
QGKGDSPEARALAKQVATALQNLQTKTNRAVANSRPAKAAVHLEGKIEQAQRWIDNPT
VDDRGVGGQAAIRGLVAEGHRLANVMMGPYRQDLLAKCDRVDQLTAQLADLAARGESES
PQARALASQLQDSLKDLKARMQEAMTQEVSDVFSDDTTPIKLLAVAATAPPDAPNREE
VFDERAANFENHSGKLGATAEKAAAVGTANKSTVEGIQASVKTARELTPQVVSAARIL
LRNPGNQAAAYEHFETMKNQWIDNVEKMTGLVDEAIDTKSLDASEEAIKKDLCKCKVA
MANIQPQMLVAGATSIARRANRILLVAKREVENSEDPKFREAVKAASDELSTISPMV
MDAKAVAGNISDPGLQKSFLDSGYRILGAVAKVREAFQPQEPDFPPPPPDLEQLRLTD
ELAPPKPLPEGEVPPPPRPPPEEKDEEFPEQKAGEVINQPMMAARQLHDEARKWSS
KGNDIIAAAKRMALLMAEMSRLVRGGSGTKRALIQCAKDIKASDEVTRLAKEVAKQC
TDKRIRTNLLQVCERIPTISTQLKILSTVKATMLGRNTNISDEESEQATEMLVHNAQNL
MQSVKETVREAEAAASIKIRTDAGFTLRWVRKTPWYQ

Figure 24. (Page 4 of 46)**M90354 Basic Transcription Factor 3 Homologue**

1 aagcttttag ttccctttaa tcataaaagc cacttgctaa ctaaaactag agatagctca
61 agctatctga ttttaaaggc ttagtctcaa tgtgtccctt cctgaaatc ccagtagagt
121 agccaattgt ctgaaacccg cttggattta gcaatgaaac acctcagtec tggccaaacc
181 aagacagtgg gtctcaggaa acattctca tcttaataaa ggcaaattaa ctacagttga
241 cccttgaaca acatgggggt tatgggtgct gacttcccat gcagtaaaaa atctgggtat
301 aactttcgat tccacaaaaa ctttgctaata agccttaact gttactgga agccttacca
361 ataacacata cagttgatta acacatatat tgtatgtatt atattacaat aaattaagct
421 agagaaaaga aaatgtattc ctttgctgc catcctgcct cctgtgtgc ttctaatctc
481 agctggtctc acccgggact cccaagtgc caaccctagt ccccaacgca gcccttttc
541 cactcagata agatgaaaga aacaatcatg aacaaaaaac tcaccaaacg gcaagcagaa
601 gtgcacactg gtcggaaagg aactgctcac aggaaaaagg tggttcacag catctgagac
661 gctgtgttg agggcaagta ggccccttg acaccttgg tgtgaactc atgaggttt
721 gaatgtccag ggacattggc caatatcaaa agaactttaa aagtcagttt ggtaaggtag
781 ttcttgactt cagggacaaa acagcaatgg aaccaatcca gaaaaagggt tctcattgtc
841 caggccttct ggtacaacca aaagactggc agctggcatt tatctgtcc ctcaaggct
901 cagagggttaa cggttttata cataagggtg gtcctgatca taaacctagc gacagcagag
961 gataaaaaat ttcagttctc cttaaagaaa ttaggggtta acaatatccc tggatttgaa
1021 gaggtgaata tgtttacaca ccaaggaaca gtgattcact ttaacaacc tgaagttcag
1081 gcacgctgg cagcaaacac tttaccatg acaggccatg ctgagacaaa gcagctgaca
1141 gaaatgctac tcagcatcga tcataaacca gtgctgcaga tggctgact agttcaaaga
1201 gactggctaa cactgcccaa acaatctgtg ggtggaaaag caccattgc tactggagag
1261 gatgatgaag ttctagatct tgtggagaat tctgatgagg ctccaacaa tgaggcaaac
1321 tgaattaagt caacttctga agaagataaa acttgaagta gttactgaga gctgctgtt
1381 tatgttatga ctgctttta aaaatgttt tgtttacaga tcttaataaa atctagatct
1441 ctaatattt

Figure 24. (Page 5 of 46)

J04111 Human c-jun proto oncogene

1 cccggggagg ggaccgggga acagagggcc gagaggcgtg cggcaggggg gagggtagga
 61 gaaagaaggg cccgactgta ggagggcagc ggagcattac ctcacccgt gagcctccgc
 121 gggcccagag aagaatcttc tagggtggag tctccatggt gacgggcggg cccgcccccc
 181 tgagagcgac gcgagccaat gggaaggcct tggggtgaca tcatgggcta ttttagggg
 241 ttgactggta gcagataagt gttgagctcg ggctggataa gggtcagag ttgactgag
 301 tgtggctgaa gcagcgaggc gggagtggag gtgcgcggag tcaggcagac agacagacac
 361 agccagccag ccaggctggc agtatagtcc gaactgcaa tcttatttc tttcacctt
 421 ctctctaaact gccagagct agcgctgtg gctccgggc tgggtgttcg ggagtgtcca
 481 gagagccttg tctccagcgc gccccgggag gagagccctg ctgccaggc gctgttgaca
 541 gcggcggaaa gcagcggtag ccacgcgc ccgcggggga cgtcggcgag cggctgcage
 601 agcaaagaac ttcccgggc gggaggaccg gagacaagtg gcagagtccc ggagcgaact
 661 ttgcaagcc ttctctgct cttaggcttc tccacggcgg taaagaccag aaggcggcgg
 721 agagccacgc aagagaagaa ggacgtcgc tcagcttcgc tcgacccgt tgttgaact
 781 gggcgagcgc gagccgcgc tccgggcgc cccctcccc tagcagcga ggaggggaca
 841 agtcgtcgga gtccggcgc ccaagaccgc ccgcggcgc gccactgcag ggtccgcact
 901 gatccgctcc gcggggagag ccgctgctct gggaagttag ttgcctgcg gactccagg
 961 aaccgtcgc cccgaagagc gctcagttag tgaccgcgc tttaaaagc cgggtagcgc
 1021 gcgcgagtcg acaagtaaga gtgcgggagg catcttaatt aacctgcgc tcctggagc
 1081 gagctggtag ggagggcga gcggggacga cagccagcgg gtgcgtgcgc tcttagagaa
 1141 actttccctg tcaaaggctc cggggggcgc ggggtgtccc cgttgccag agccctgttg
 1201 cggccccgaa acttgtgcgc gcacgcaaa ctaacctcac gtgaagttag ggactgttct
 1261 atgactgcaa agatggaac gacctctat gacgatgcc tcaacgcctc gttctccc
 1321 tccgagagcg gaccttatgg ctacagtaac cccaagatcc tgaacagag catgacctg
 1381 aacctggccg acccagtgga gagcctgaag ccgcacctcc gcgccaagaa ctcggacctc
 1441 ctcacctgc ccgacgtggg gctgtcaag ctggcgtgc ccgagctgga gcgctgata
 1501 atccagtcca gcaacgggca catcaccacc acgcccaccc ccaccagtt cctgtgccc
 1561 aagaacgtga cagatgagca ggagggggtc cccgagggct tegtgcgcgc cctggccgaa
 1621 ctgcacagcc agaacacgt gccacgcgc acgtcggcgg gcagccgggt caacggggca
 1681 ggcatggtag ctcgcgggt agcctcgggt gcagggggca gcggcagcgg cggttcagc
 1741 gccagcctgc acagcgagcc gccggtctac gcaaacctca gcaactcaa cccaggcgcg
 1801 ctgagcagcg gcggcggggc gccctctac ggcgcgccgc gcctggcctt tccgcgcaa
 1861 cccagcagc agcagcagcc gccgcaccac ctgcccagc agatgcccgt gcagcaccg
 1921 cggctgcagg cctgaagga ggagcctcag acagtgcgc agatgcccgg cgagacaccg
 1981 cccctgtccc ccatgacat ggagtcccag gagcggatca aggcggagag gaagcgcag
 2041 aggaaccgca tcgtgcctc caagtccga aaaaggaaagc tggagagaat cggccggctg
 2101 gaggaaaaag tgaaaacctt gaaagctcag aactcggagc tggcgtccac ggccaacatg
 2161 ctcagggaac aggtggcaca gcttaaacag aaagtcata accacgttaa cagtgggtgc
 2221 caactcatgc taacgcagca gttgcaaca tttgaagag agaccgtcg gggctgaggg
 2281 gcaacgaaga aaaaaataa cacagagaga cagacttgag aacttgaca gttgcgacgg
 2341 agagaaaaaa gaagtgtccg agaactaaag ccaagggtat ccaagttgga ctgggttcgg
 2401 tctgacggcg ccccgagtg gcacgagtg gaaggacttg gtcgcgcct ccttggcgt
 2461 ggagccaggg agcggccgc tgcgggctgc ccgcttgc ggacgggctg tcccgcgcg
 2521 aacggaactg tggacttcg ttaacattga ccaagaactg catggacct acattcgatc
 2581 tcattcagta ttaaggggg gagggggagg gggttcaaa ctgcaataga gactgtagat
 2641 tgcttctgta gtactccta agaacacaaa gcggggggag ggttggggag gggcggcagg
 2701 agggaggttt gtgagagcga ggctgagcct acagatgaac tcttctggc ctgcttctg
 2761 taactgtgta tgcacatata tatattttt aatttgatta aagctgatta ctgtcaataa

Figure 24. (Page 6 of 46)

2821 acagcttcat gcctttgtaa gttatttctt gtttgtttgt ttgggtatcc tgcccagtgt
2881 tgtttgtaaa taagagattt ggagcactct gagttacca ttgtataaa agtatataat
2941 tttttatgt ttgtttctg aaaattccag aaaggatatt taagaaaata caataaacta
3001 ttggaaagta ctcccctaac ctctttctg catcatctgt agatcctagt ctatctaggt
3061 ggagttgaaa gagttaagaa tgctcgataa aatcactctc agtgcttctt actattaagc
3121 agtaaaaact gttctctatt agacttagaa ataaatgtac ctgatgtacc tgatgctatg
3181 tcaggettca tactccacgc tccccagcg tatctatatg gaattgctta ccaaaggcta
3241 gtgcgatgtt tcaggaggct ggaggaaggg gggttgcagt ggagaggac agcccactga
3301 gaagcaaac atttcaaagt ttggattgca tcaagtggca tgtgctgtga ccatttataa
3361 tgtagaaaat ttacaatag gtgcttattc tcaaagcagg aattggtggc agattttaca
3421 aaagatgtat cttccaatt tggatcttc tcttgacaa ttctagata aaaagatggc
3481 ctttgtctta tgaatatta taacagcatt ctgcacaat aaatgtattc aaataccaat
3541 aacagatctt gaattgcttc ctttactac tttttgttc ccaagttata tactgaagtt
3601 tttatttta gttgctgagg tt

Figure 24. (Page 7 of 46)**K00650 Human c-fos proto-oncogene**

1 gcaggaacag tgctagtatt gctcgagccc gagggctgga ggtagggga tgaaggctg
 61 ctccacgct ttgactgaa ttagggctag aattggggat gggggtaggg gcgcattcct
 121 tggggagcgg aggttaagt cctcggggtc ctgtactga tgcgtttct cctatctctg
 181 agcctcagaa ctgtttcag ttccgtaca agggtaaaaa ggcgtctct gccccatccc
 241 ccccgacct gggaacaagg gtccgcattg aaccagggtc gaatgtctc tctattctg
 301 cgccgtccc gcctcccct ccccgccgc ggccccgcc tcccccgca ctgcaccctc
 361 ggtgttgct gcagcccgcg agcagttccc gtcaatccct cccccctac acaggatgtc
 421 catattagga catctgcgc agcaggttc cacggcctt cctgtagcc ctggggggag
 481 ccatccccg aacccctcat ctggggggc ccacgagacc tctgagacag gaactgcgaa
 541 atgtcacga gattaggaca cgcgccaagg cgggggcagg gagctgcgag cgctggggac
 601 gcagccgggc ggccgcagaa gcgcccaggc ccgcgcgcca cccctctggc gccaccgtgg
 661 ttgagcccg gacgtttaca ctattcata aaacgcttg tataaaagca gtggtctcgg
 721 cgcctctac tccaaccgca tctgcagca gcaactgaga agccaagact gagccggcgg
 781 ccgcggcgca gcgaacgagc agtgaccgtg ctctaccca gctctgttc acagcgcca
 841 cctgtctcg cccctcgcc cctcgccgg cttgcctaa ccgccacgat gatgttctg
 901 ggcttcaac cagactcga ggcgtcatc tcccgctga gcagcgcgc cccggccggg
 961 gatagcctt ctactacca ctacccgca gactcctt ccagcatggg ctgcctgtc
 1021 aacgcgcagg taaggctggc tcccgtcg cgcggggcgg ggggcttggg gtcgcggagg
 1081 aggagacacc gggcgggacg ctccagtaga tgagtagggg gctccctgt gcctggaggg
 1141 aggtgccgt ggccggagcg gtgcccgtc gggggctcgg gacttgcct gagcgcacgc
 1201 acgttgcca tagtaagaat tggttcccc ttcgggaggc aggttcgtc tgagaaacct
 1261 ctggtctga ctccaggacg gatctctgac attagctgga gcagacgtg cccaagcaca
 1321 aactcgtaa ctagagcctg gcttctcgg ggagggtgga gaaagcggca atccccctc
 1381 cccggcagc ctggagcagc gaggaggat gaggaggag ggtgcagcgg gcgggtgtgt
 1441 aaggcagtt cattgataaa aagcgagtc attctggaga ctccggagcg gcgcctgcgt
 1501 cagcgagac gtcagggata ttataacaa acccccttc aagcaagtga tgctgaaggg
 1561 ataacgggaa cgcagcggca ggatggaaga gacaggcact gcgtgcgga atccctggga
 1621 ggaaaagggg gagaccttc atccaggatg agggacattt aagatgaaat gtccgtggca
 1681 ggatcgttc tcttactgc tgcagcggc actgggaact cgcaccacct gtgtccgga
 1741 cctgctcgt cacgtcggc tccccctt gtttgttct aggaactctg cacggacctg
 1801 gccgtctca gtgccaact cattcccacg gtcactgcca tctgaccag tccggacctg
 1861 cagtggctgg tgcagccgc cctcgtctc tctgtgccc catcgagac cagagccct
 1921 cacccttcg gagtccccg cccctccgt ggggcttact ccagggtgg cgttgtgaag
 1981 accatgacag gagccgagc gcagagcatt ggcaggaggg gcaagggtga acaggtagg
 2041 aactctagc tactcttct gggaatgtg ggcgtgggtg ggaagcagc ccggagatgc
 2101 aggagcccag tacagaggat gaagccactg atggggctgg ctgcacatc gtaactggga
 2161 gccctggct caagccatt ccatcccaac tcagactctg agtctaccc taagaagtac
 2221 tctcatagt tctccctaa gtttctacc gcatgcttc agactgggt cttcttgtt
 2281 ctcttctga ggatcttatt ttaaatgaa gtcacaccta tctgcaact gcaggtcaga
 2341 aatggttca cagtgggtg ccaggaagca gggaagctgc aggagccagt tctactggg
 2401 tgggtgaat gaggtgatg cagacactt tactgaatg cgtctttt ttgtgattat
 2461 tctagttat ccagaagaa gaagagaaaa ggagaatccg aagggaagg aataagatg
 2521 ctgcagcaa atcccgcaac cggaggagg agctgactga tacactcaa gcggtagga
 2581 ctctgtggg tctcctttt taaacttaa gggaaagt gagattgagc ataaggccc
 2641 ttgagtaaga ctgtgttta tcttctct taccctctg tatacaggag acagaccaac
 2701 tagaagatga gaagtctgt ttgcagacc agattgcaa cctgtgaag gagaaggaaa
 2761 aactagagtt catcctggca gtcaccgac ctgcctgca gatccctgat gacctgggt

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2821 tcccagaaga gatgtctgtg gcttcccttg atctgactgg gggcctgcc aagggttgcca
2881 ccccgagtc tgaggaggcc ttcacctgc ctctcctcaa tgacctgag cccaagccct
2941 cagtggaaacc tgtcaagagc atcagcagca tggagctgaa gaccgagccc ttgatgact
3001 tcctgttccc agcatcatcc agggccagtg gctctgagac agcccgtcc gtgccagaca
3061 tggacctatc tgggtccttc tatgcagcag actgggagcc tctgcacagt ggctccctgg
3121 ggatggggcc catggccaca gagctggagc cctgtgcac tccggtggtc acctgtactc
3181 ccagctgcac tgcttacacg tcttcttcg tcttcaccta ccccgaggct gactccttc
3241 ccagctgtgc agctgcccac cgcaagggca gcagcagcaa tgagccttc tctgactgc
3301 tcagctcacc cacgtgctg gccctgtgag ggggcaggga aggggaggca gccggcaccc
3361 acaagtcca ctgccgagc tgggtcatta cagagaggag aaacacatct tcctagagg
3421 gttcctgtag acctagggag gacctatct gtgcgtgaaa cacaccaggc tgtgggcctc
3481 aaggactga aagcatccat gtgtggactc aagtccttac ctctccgga gatgtagcaa
3541 aacgatgga gtgtgtattg ttccagtga cactcagag agctggtagt tagtagcatg
3601 ttgagccagg cctgggtctg tgtctcttt ctcttctcc ttgtctct catagcatta
3661 actaatctat tgggttcatt attgaatta acctggtgct ggatatttc aaattgtatc
3721 tagtgcagct gattttaaca ataactactg tgttctggc aatagtgtg tctgattaga
3781 aatgaccaat attatactaa gaaaagatac gactttatt tctggtagat agaaataaat
3841 agctatatcc atgtactgta gttttcttc aacatcaatg ttcattgtaa tgttactgat
3901 catgcattgt tgagggtgct tgaatgtct gacattaaca gtttccatg aaaacgttt
3961 attgtgttt taatttatt attaagatgg attctcagat atttatatt ttattttat
4021 ttttctacc ttgaggtcct ttgacatgtg gaaagtgaat tgaatgaaa aatttaagca
4081 ttgtttgctt attgttcaa gacattgtca ataaaagcat ttaagttaa tgcgaccaac
4141 ctgtgctct ttcattctg gaagtctgt aagttctga aaggtattat tggagaccag
4201 ttgtcaaga aggttagctg ctggaggggg acacaccctc tgtctgatcc ctatcaaaag
4261 aggacaagga aactatagag ctgattttag aatattttac aaatacatgc ctccattgg
4321 aatgctaaga tttctactg ctctgggga cggggaaaccg ctgtgtaaca gctttgtgg
4381 gaatacatt tttctgttc agtactcgca gggggaaata ttaaatttt gtgtgctaa
4441 tattaatc agatgtttg atcttaaagg aacctttta gcaaacagaa cctagcttg
4501 tacagactat ttaactttt tattctcaca aaatcacgtg gagggttatt ctactcaaa
4561 gatgagcaaa tgaagaatg gtagaataa acaacttct tgatattccg ttatcggc
4621 tagaatctc ctgctcgta tctatccag caggctgaac tgcctctga tacttggtta
4681 aaaaaaatt tcaggccggg cgcggtggcc catgcctgta atcctagcac ttgggaggc
4741 cgaggcaggc ggatcacctg aggtcgggag ttcgagacca gcctgacca catggagaaa
4801 cccgtcttt actaaaata caaaattagc ctggtgtggt ggtgcatgcc tgaatccta
4861 gctacttgag aggtgagac aggaataca ctgaactcg ggaggcggat gttgcagcga
4921 actgagattg gcctattgca ctccagcctg ggcaacaaga ttgaaactct gttaaaaaa
4981 aaaagtctt actaatgtg acatttttt gtactcttt attctgaaa gggaaggagg
5041 gctattgccc tatcccttat taataatgc attgtggtt ctggtttct taataccata
5101 tgccttcat tcagtttata gtggcgaggaa gtgggggaga aaaagtgtc cagaaatcaa
5161 aagatatctc aaacagcaca aataatggct gatcgtctg caaacaaaaa gttacataat
5221 agtcaagaa ggagaagtca acatgactct gaacaagctt taactagaa actttatcat
5281 ctaagggaag aacgtgacct ttgtccagga cgtctctggt aatggggcac ttacacacac
5341 atgcacagt acaaacaca gggaaaggag accgccctc tgcctctgct cgcgagtac
5401 acgaggcac catgcactat gtttcacac aactgggtg gaagaagagc ttacgcgcca
5461 gtcttcta atgtttgtga taatgaaaat cactgggtgc ttatggggtg tcatattcaa
5521 tcgagttaa agttttaatt caaatgaca gttttactga ggtgatgtt ctgtctatg
5581 atatctctgc cctcccata aaaatggaca tttaaaagca acttaccgct cttagatca
5641 ctctatatc acacaccact tgggtgctg ttctgctag acttgtgatg acagtggcct
5701 taggatccct gtttctgtt caaagggcaa atattttata gcctttaa atacctaac

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5761 taaatacaga attaataaa ctaacaaaca cctggtctga aataacaagg tgatctacc
5821 tggaaggaaac ccagctgggtg ggccaggagc ggtggctcac acctgtaatt ccagcactt
5881 gggaggctga gacaggagga tctctggagt ccaggagttt gagaccagcc tgggcaacat
5941 ggcaaaaccc agtgtgttc tgtgtcca gctacactac tcaggaggct gaggcaggag
6001 tatgactga gcctgggagg gggagggtgc agagaactga tattgcacca ccactgcact
6061 ccagcctggg tgacacagca aaacctatc tcaaaaaaa aaaaaaaaaa aaggaacca
6121 gctggttct gtaggtgtgc aataataaca accagaggaa gaaaaggaag acgattccc
6181 agatgaagaa gggcagctgg acctcggac

Figure 24. (Page 10 of 46)**NM 080422 Homo Sapiens Protein Tyrosine Phosphatase, non-receptor type 2**

1 gctcgggcg cagctctgcg cgctgacgtc cgacgtcca ggtacttcc ccacggccga
61 cagggcttgg cgtgggggcg gggcgcgcg cgacgcgcgc atgcgccgca gcgccagcgc
121 tctccccgga tcgtgcgggg cctgagcctc tccgccggcg caggctctgc tcgccagcgc
181 tcgctccgc agccatgcc accaccatcg agcgggagtt cgaagagttg gatactcagc
241 gtcgctggca gccgctgtac ttggaatc gaaatgagtc ccatgactat cctcatagag
301 tggccaagtt tccagaaaac agaaatcgaa acagatacag agatgtaagc ccatatgac
361 acagtctgt taaactgcaa aatgctgaga atgattatat taatgccagt ttagtgtaca
421 tagaagaggc acaaaggagt tacatctaa cacagggtcc acttcctaac acatgctgcc
481 attctggct tatggttgg cagcagaaga ccaaagcagt tgtcatgctg aaccgcattg
541 tggagaaaga atcggttaaa tgtgcacagt actggccaac agatgaccaa gagatgctgt
601 ttaagaaac aggattcagt gtgaagctct tgcagaaga tgtgaagtcg tattatacag
661 tacatctact acaattagaa aatatcaata gtggtgaaac cagaacaata tctcacttc
721 attatactac ctggccagat ttggagtc ctgaatcacc agcttcattt ctcaattct
781 tgtttaaagt gagagaatct ggctcctga accctgacca tgggcctgcg gtgatccact
841 gtagtgcagg cattgggcgc tctggcacct tctctctgt agacactgt cttgtttga
901 tggaaaaagg agatgatatt aacataaaac aagtgttact gaacatgaga aaataccgaa
961 tgggtcttat tcagacccca gatcaactga gattctcata catggctata atagaaggag
1021 caaatgtat aaaggagat tctagtatac agaaacgatg gaaagaactt tctaaggag
1081 acttatctcc tgccttggat cattcaccaa acaaaataat gactgaaaaa tacaatggga
1141 acagaatagg tctagaagaa gaaaaactga caggtgaccg atgtacagga ctttctcta
1201 aaatgcaaga tacaatggag gagaacagt agagtgtct acggaaacgt attcgagagg
1261 acagaaaggc caccacagct cagaagggtc agcagatgaa acagaggcta aatgagaatg
1321 aacgaaaaag aaaaaggcca agattgacag acacctaata ttcatgactt gagaatattc
1381 tgcagctata aatttgaac cattgatgtg caaagcaaga cctgaagccc actccggaaa
1441 ctaaagttag gctcgctaac cctctagatt gctcacagt tgtttgtta caaagtaaac
1501 ttacatcca ggggatgaag agcaccacc agcagaagac ttgcagaac ctttaattgg
1561 atgtgttaag tgttttaaat gagtgtatga aatgtagaaa gatgtacaag aaataaatta
1621 ggagagatta cttgtattg tactgccatt cctactgtat tttatactt tttggcagca
1681 taaatattt ttgttaata aaaaaaaaaa aaaa

Figure 24. (Page 11 of 46)**M68520 Human cdc2-related protein kinase**

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1 ggagggcgca acattgttc aagttggcca aattgacaag agcgagaggt atactgcgtt
61 ccattccgac ccgggccacg gtactgggcc ctgtttcccc ctctcggcc cccgagagcc
121 aggggtccgc ttctgcaggg ttcccaggcc cccgctccag ggccgggctg acccgactcg
181 ctggcgcttc atggagaact tccaaaaggt ggaaaagatc ggagagggca cgtacggagt
241 tgtgtacaaa gccagaaaca agttgacggg agaggtgggt gcgcttaaga aaatccgcct
301 ggacactgag actgaggggtg tgcccagtac tgccatccga gagatctctc tgcttaagga
361 gcttaacat cctaatttg tcaagctgct ggatgtcatt cacacagaaa ataaactcta
421 cctggttttt gaattctgc accaagatct caagaaatc atggatgcct ctgctctcac
481 tggcattcct ctccctcca tcaagagcta tctgtccag ctgctccagg gcctagcttt
541 ctgcattct catcggtcc tcaccgaga ccttaacct cagaatctgc ttattaacac
601 agagggggcc atcaagctag cagactttgg actagccaga gcttttgag tcctgttctg
661 tacttacacc catgaggtgg tgacctgtg gtaccgagct cctgaaatcc tcctgggctg
721 caaatattat tccacagctg tggacatctg gagcctgggc tgcatctttg ctgagatggt
781 gactcgccgg gcctattcc ctggagattc tgagattgac cagctcttcc ggatctttcg
841 gactctgggg accccagatg aggtgggtgt gccaggagt attctatgc ctgattacaa
901 gccaaagttc ccaagtggtg cccggcaaga ttttagtaaa gttgtacctc cctgggatga
961 agatggacgg agcttggtat cgcaaatgct gcactacgac ctaacaagc ggatttcggc
1021 caaggcagcc ctggctcacc ctttctcca ggatgtgacc aagccagtac ccatcttctg
1081 actctgatag ccttctttaa gccccagcc ctaatctcac cctctcctcc agtgtgggct
1141 tgaccaggct tgcgttggg ctatttgac tcaggtgggc cctctgaact tgcctaaac
1201 actcaccttc tagtcttggc cagccaactc tgggaatata ggggtgaaag gggggaacca
1261 gtgaaatga aagggaagtt cagtattaga tgcacttaag ttgacctcca ccacccttc
1321 ccccttctct tagttattgc tgaagagggt tggataaaaa ataattttaa aaaagccttc
1381 ctacacgtta gatttgccgt accaatctct gaatgcccc taattattat ttccagtgt
1441 tgggatgacc aggatcccaa gcctctgct gccacaatgt ttataaaggc caaatgatag
1501 cgggggctaa gttggtgctt ttgagaacca agtaaaacaa aaccactggg aggagtctat
1561 tttaaagaat tcggttgaaa aaaatagatc caatcagttt atacctagt tagtgtttg
1621 cctcacctaa taggctggga gactgaagac tcagcccggg tggctgcaga aaaatgattg
1681 gcccagtcct cctgtttgt ccttctaca ggcatgagga atctgggagg ccctgagaca
1741 gggattgtgc ttattccaa tctattgct caccatggcc ttatgaggca ggtgagagat
1801 gttgaattt ttcttctct ttagtattc ttagtgttc agttgccaag gatccctgat
1861 cccattttcc tctgacgtcc acctctacc ccataggagt tagaagttag ggtttaggca
1921 tcattttgag aatgctgaca cttttcagg gctgtgattg agtgagggca tgggtaaaaa
1981 tatttcttta aaagaaggat gaacaattat atttatattt caggttatat ccaatagtag
2041 agttggcttt tttttttt ttttgctat agtgggtgga ttgttgcca tgtgcacctt
2101 ggggtttgtt aatgacagtg ctaaaaaaaaa agcattttt tttatgatt tgtctctgtc
2161 accctgtccc ttgagtctc ttgctattaa cgttattgt aatttagttt gta

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Figure 24. (Page 12 of 46)**M74091 Human Cyclin C**

1 gagcgcgggt accggacggg ctgggtctat ggctgctccg cggccgctcc gccgcgtggt
61 gctttttat cagggcaagc tgtgttccat ggcagggaac ttttggcaga gctcccacta
121 ttgcaatgg attttgata aacaagatct gttgaaggag cgccaaaagg atttaaagtt
181 tcttcagag gaagaatatt ggaagtaca aatattttt acaaatgtta tccaagcatt
241 aggtgaacat cttaaataa gacaacaagt tattgccact gctacggtat attcaagag
301 attctatgcc aggtattctc tgaaaagtat agatcctgta ttaatggctc ctacatgtgt
361 gttttggca tccaaagtag aggaatttg agtagttca aatacaagat tgattgctgc
421 tgctactct gtattaaaa ctagatttc atatgcctt ccaaaggaat ttcttatag
481 gatgaatcat atattagaat gtgaattcta tctgttagaa ctaatggatt gttgcttgat
541 agtgtatcat ccttatagac ctttgcctca gtatgtgcag gacatgggcc aagaagacat
601 gttgctccc ctgcatgga ggatagtga tgatacctac agaacggatc ttgcctact
661 gtatcctct tcatgatag ctttagctg cctacatgta gcctgtgttg tacagcagaa
721 agatgccagg caatggttg ctgagcttc tgtggatatg gaaaagattt tggaaataat
781 cagggttatt taaaactat atgagcagt gaagaattc gatgagagaa aagagatggc
841 aaccattctt agtaagatgc caaaaccaa accacctcca aacagtgaag gagagcaggg
901 tccaaatgga agtcagaact ctactacag ccaatctaa aacattccga agaattccat
961 agtggaccac ttggaataa accattggac agatttcagt aatgtctca gtggaacaca
1021 aatgaaaatg aatagctgt ttctgtcaag catattggaa agtgatttta ttttgcaa
1081 tagttttct ttaatgat tctagtacat aattgattga taaatctct tgattataa
1141 tgtttgaaa ggttctaagg ggacctacag acagacatac atagacattt caaaattaat
1201 agcttttgat tagtataata ttcttaatt tggataataa aaattgtagc ttttattaa
1261 gccaggaaac atgaagcata attgtttta aattctctt ggtcattgag ggacaaaaa
1321 aggacgtaaa atttacagtc aatctatgag ggttttttc cctccataag ttaacttta
1381 aaactgtatt taaggaatca aatcttaca aatcctggaa gattttgga atgatgtga
1441 taatttcagg gaaattaatc aagtaccgta tattgattta aaagtgtatt ttattcagta
1501 gtttgagg

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U60325 Human DNA polymerase gamma

1 aggatttggg gtggaaggca ggcattgtca acccatgtca ctgacaggag agcagagaca
 61 gacgtgtctc tctccacgtc ttccagccag taaaagaagc caagctggag cccaaagcca
 121 ggtgttctga ctcccagcgt ggggggtcct gcaccaacca tgagccgcct gctctggagg
 181 aaggtggccg gcgccaccgt cgggccaggc cgggtccag ctccggggcg ctgggtctcc
 241 agtcccgcc cgcgtccga cccagcgcac gggcagcggc ggcggcagca gcagcagcag
 301 cagcagcagc agcagcaaca gcagcctcag cagccgcaag tgctatctc ggaggcgagg
 361 cagctgcggc acaaccatt ggacatccag atgctctcga gagggtgca cgagcaaatc
 421 ttcgggcaag gaggggagat gcttggcgag gccgcggtgc gccgcagcgt cgagcacctg
 481 cagaagcacg ggcctctggg gcagccagcc gtgcccttgc ccgacgtgga gctgcgctg
 541 ccgccccctc acgggggaca cctggaccag cacttccgcc tctggccca gaagcagagc
 601 ctgccctacc tggaggcggc caacttctg ttgcaggccc agctgcccc gaagccccg
 661 gcttgggctt gggcgaggag ctggaccggg tacggcccc aggggggagg cgtaccctg
 721 gccatcccc aggagcgggc cctggtgttc gacgtggagg tctgcttggc agagggaact
 781 tgccccacat tggcggtggc catatcccc tcggcctggt attcctgtg cagccagcgg
 841 ctggtggaag agcgttactc ttggaccagc cagctgtcgc cggctgacct catccccctg
 901 gaggtcccta ctggtgccag cagccccacc cagagagact ggcaggagca gttagtgtg
 961 gggcacaatg ttctcttga ccgagctcat atcaggagc agtacctgat ccagggttcc
 1021 cgcattgcgt tcttgacac catgagcatg cacatggcca tctcagggt aagcagctt
 1081 cagcgcagtc tgtggatagc agccaagcag ggcaaacaca aggtccagcc ccccaaaag
 1141 caaggccaga agtcccagag gaaagccaga agaggcccag cgatctcatc ctgggactgg
 1201 ctggacatca gcagtgtcaa cagtctggca gaggtgcaca gactttatgt aggggggcct
 1261 cccttagaga aggagcctcg agaactgtt gtgaagggca ccatgaagga cattctgag
 1321 aactccagg acctgatgca gtactgtcc caggacgtg gggccacca tgaggtttc
 1381 cagcagcagc taccgtctt ctggagagg tgtccccacc cagtactct gcccgcatg
 1441 ctggagatgg gtgtctcta cctgcctgtc aaccagaact gggagcgta cctggcagag
 1501 gcacagggca cttatagga gctccagcg gagatgaaga agtcgttgat ggtctggcc
 1561 aatgatgect gccagctgt ctacggagag aggtacaaag aagaccctg gctctgggac
 1621 ctggagtggg acctgcaaga atttaagcag aagaaagta agaagggtga gaaggaacca
 1681 gccacagcca gcaagttgcc catcgagggg gctggggccc ctggtgatcc catggatcag
 1741 gaagacctcg gccccgcag tgaggaggag gagtttcaac aagatgtcat gggccgcgc
 1801 tgcttgcaag agctgaagg gaccacagag ctctgcccc agcgccccca gcaccttct
 1861 ggacacctg gatggtacc gaagctctgc ccccggttag acgacctgc atggacccg
 1921 ggccccagcc tctcagcct gcagatcgg gtcacaccta aactcatggc acttacctg
 1981 gatggttcc ctctgacta ctacagcgt catggctgg gctacttgg cctgggagg
 2041 cgggacaacc tggccaagct gccgacagg accaccctgg agtcagctg ggtggtctg
 2101 ccctacagag ccatcgagtc cctgtacagg aagcactgtc tcgaacagg gaagcagcag
 2161 ctgatgccc aggaggccg cctggcggag gagttctgc tactgacaa tagtgccata
 2221 tggcaaacgg tagaagaact ggattacta gaagtggagg ctgaggccaa gatggagaac
 2281 ttgcagctg cagtgccagg tcaacccta gctctgactg cccgtggtgg cccaaggac
 2341 acccagccca gctatcaca tggcaatgga ccttacaac agctggacat ccttggtgc
 2401 tggttttca agctgctca caaggatgt aatagctgta atgtgggaag ccccttggc
 2461 aaggacttcc tgcccaagat ggaggtggc accctgcagg ctggcccagg aggtgccagt
 2521 gggccccgtg ctctggaaat caacaaaatg atttcttct ggaggaaag ccataaacg
 2581 atcagctccc agatggtggt gtggtgccc aggtcagctc tgccccgtg tgtatcagg
 2641 caccctgact atgatagga aggcctctat ggggccatcc tgcccaagt ggtgactgc
 2701 ggcacatca ctgcggggc tgggagccc acatggtca ccgccagca tgcccgcc
 2761 gaccgagtag gcagtgaatt gaaagccatg gtgcaggccc cactggcta caccctgtg

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2821 ggtgctgatg tggactccca agagctgtgg attgcagctg tgcttgaga cgccacttt
2881 gccggcatgc atggctgcac agcctttggg tggatgacac tgcagggcag gaagagcagg
2941 ggcactgac tacacagtaa gacagccact actgtgggca tcagccgtga gcatgccaaa
3001 atctcaact acggccgcat ctatggtgct gggcagccct ttgctgagcg ctactaatg
3061 cagttaacc accggctcac acagcaggag gcagctgaga aggcccagca gatgtacgt
3121 gccaccaagg gcctccgctg gtatcggctg tcgcatgagg gcgagtggct ggtgagggag
3181 ttgaacctcc cagtggacag gactgagggt ggctggattt ccctgcagga tctgcgcaag
3241 gtccagagag aaactgcaag gaagtcacag tggagaagt gggaggtggt tgctgaacgg
3301 gcatggaagg ggggcacaga gtcagaaatg tcaataagc ttgagagcat tgctacgtct
3361 gacataccac gtaccccggt gctgggctgc tgcacagcc gagccctgga gcctcggct
3421 gtccaggaag agtttatgac cagccgtgtg aattgggtgg tacagagctc tgctgtgac
3481 tacttacacc tcatgctgtt ggccatgaag tggctgttg aagagttgc catagatggg
3541 cgcttctgca tcagcatcca tgacgaggtt cgctacctgg tgcgggagga ggaccgtac
3601 cgcgctgccc tggccttgca gatcaccaac ctcttgacca ggtgcatgtt tgcctacaag
3661 ctgggtctga atgactgcc ccagtcagtc gccttttca gtgcagtcga tattgaccgg
3721 tgcctcagga aggaagtgac catggattgt aaaaccctt ccaaccaac tgggatggaa
3781 aggagatacg ggattcccca ggggaagcg ctggatattt accagataat tgaactacc
3841 aaaggctcct tggaaaaacg aagccagcct ggaccatagc actgcctgga ggctctgtat
3901 ttgctccgt ggagcttcat cggggtgtg caggctccca aactcaggct tcagctgtg
3961 cttttgcaa aagggttgc taaggccagc cattttcag tagcaggacc tgccaagaag
4021 attcctcta actgaagggtg cagttgaatt cagtgggtc agaaccaaga tgccaacatc
4081 ggtgtggact acaggacaag gggcattgtt gctgttggg taaaatgaa gcagaagccc
4141 caaagttcac attaaactcag gcatttcatt ttttttcc tttctctt ggctggttct
4201 ttgtctgtc cccatgctc tgatgcagtc ccctagaagg ggaaagaatt aatgctctaa
4261 cgtgataaac ctgctcaag gcagtggaaa taaaagaag gaaaaaaaaa aaaaaaaaaa

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X52479 Protein Kinase C alpha

1 ggagcaagag gtggttgggg ggggaccatg gctgacgttt tcccgggcaa cgactccacg
 61 gcgtctcagg acgtggccaa ccgcttcgcc cgcaaagggg cgctgaggca gaagaacgtg
 121 cagcaggtga aggaccacaa attcatcgcg cgcttctca agcagcccac cttctgcagc
 181 cactgcaccg acttcatctg ggggtttggg aaacaaggct tccagtgcc aagtttctgt
 241 tttgtgtcc acaagagggt ccatgaattt gttactttt ctgtccggg tgcggataag
 301 ggacccgaca ctgatgaccc caggagcaag cacaagtca aaatccacac ttacggaagc
 361 cccaccttct gcgatcactg tgggtcactg ctctatggac ttatccatca agggatgaaa
 421 tgtgacacct gcgatatgaa cggtcacaag caatgcgtca tcaatgtccc cagcctctgc
 481 ggaatggatc acactgagaa gagggggcgg atttacctaa aggcctgaggt tgcctgatga
 541 aagctccatg tcacagtacg agatgcaaaa aatctaatac ctatggatcc aaacgggctt
 601 tcagatcctt atgtgaagct gaaacttatt cctgatccca agaataaag caagcaaaaa
 661 accaaaacca tccgtccac actaaatccg cagtggatg agtcctttac attcaaattg
 721 aaaccttcag acaaagaccg acgactgtct gtagaatct gggactggga tgaacaaca
 781 aggaatgact tcatgggac ctttctttt ggagtttcgg agctgatgaa gatcccgcc
 841 agtggatggt acaagttgct taaccaagaa gaaggtgagt actacaacgt accattccg
 901 gaaggggacg aggaaggaaa catggaactc aggcagaaat tcgagaaagc caaacttggc
 961 cctgctggca acaaagtcac cagtccctct gaagacagga aacaaccttc caacaacctt
 1021 gaccgagtga aactcacgga ctcaatttc ctcatggtgt tgggaaaggg gagttttgga
 1081 aaggtgatgc ttccgacag gaagggcaca gaagaactgt atgcaatcaa aatcctgaag
 1141 aaggtatgtg tgattcagga tgatgacgtg gactgcacca tggtagaaaa gcgagtcttg
 1201 gccctgcttg acaaaccccc gttcttgacg cagctgcaact cctgcttcca gacagtggat
 1261 cggctgtact tcgtcatgga atatgtcaac ggtggggacc tcattgtacca cattcagcaa
 1321 gtaggaaaaa ttaaggaaac acaagcagta ttctatgcgg cagagatttc catcgattg
 1381 ttctttcttc ataaaagagg aatcatttat agggatctga agttagataa cgtcatgttg
 1441 gattcagaag gacatatcaa aattgctgac ttgggatgt gcaaggaaca catgatggat
 1501 ggagtcacga ccaggacett ctgtgggact ccagattata tcgccccaga gataatcgct
 1561 tatcagccgt atggaaaatc tgtggactgg tgggcctatg gcgtcctgtt gtatgaaatg
 1621 cttgccgggc agcctccatt tgatggtgaa gatgaagacg agctatttca gtctatcatg
 1681 gagcacaacg ttctctatcc aaaatccttg tccaaggagg ctgtttctat ctgcaaagga
 1741 ctgatgacca aacaccagc caagcggctg ggctgtgggc ctgaggggga gagggacgtg
 1801 agagagcatg ccttcttcg gaggatcgac tgggaaaaac tggagaacag ggagatccag
 1861 ccaccattca agcccaaagt gtgtggcaaa ggagcagaga actttgacaa gttcttcaca
 1921 cgaggacagc ccgtcttaac accacctgat cagctggtta ttgctaacaat agaccagtct
 1981 gattttgaag ggttctcgta tgtcaacccc cagtttgtgc acccatctt acagagtgca
 2041 gtatgaaact caccagcgag aacaaacacc tcccagccc ccagccctcc ccgcagtgga
 2101 agtgaatcct taaccctaaa attttaaggc caggcctgt gtctgattcc atatggaggc
 2161 ctgaaaattg tagggttatt agtccaaatg tgatcaactg ttcagggtct ctctcttaca
 2221 accaagaaca ttatcttagt ggaag

Figure 24. (Page 16 of 46)**D00017 Lipocortin II/Annexin A2**

1 catttgggga cgctctcagc tctcggcgca cggcccagct tcctcaaaa tgtctactgt
61 tcacgaaatc ctgtgcaagc tcagcttgga gggatgacac tctacacccc caagtgcata
121 tgggtctgtc aaagcctata ctaacttga tgctgagcgg gatgcttga acattgaaac
181 agccatcaag accaaagggtg tggatgaggt caccattgtc aacatttga ccaaccgcag
241 caatgcacag agacaggata ttgccttcgc ctaccagaga aggacaaaa aggaacttgc
301 atcagcactg aagtcagcct tatctggcca cctggagacg gtgattttg gcctattgaa
361 gacacctgtc cagtatgacg cttctgagct aaaagcttc atgaaggggc tgggaaccga
421 cgaggactct ctattgaga tcactgtctc cagaaccaac caggagctgc aggaaattaa
481 cagagtctac aaggaaatgt acaagactga tctggagaag gacattatt cggacacatc
541 tggtagcttc cgcaagctga tggttgccct ggcaaagggt agaagagcag aggatggctc
601 tgcattgat tatgaactga ttgaccaaga tgctcgggat ctctatgacg ctggagtga
661 gaggaagga actgatgttc ccaagtggat cagcatcatg accgagcgga gcgtgcccc
721 cctccagaaa gtatttgata ggtacaagag ttacagccct tatgacatgt tggaaagcat
781 caggaaagag gttaaaggag acctggaaaa tgcttcctg aacctggctc agtgattca
841 gaacaagccc ctgtattttg ctgatcggct gtatgactcc atgaaggga aggggacgcg
901 agataaggct ctgatcagaa tcattgtctc ccgcagtga gtggacatgt tgaataatg
961 gtctgaattc aagagaaagt acggcaagtc cctgtactat tatatccagc aagacactaa
1021 gggcgactac cagaaagcgc tgctgtacct gtgtggtgga gatgactgaa gcccgcacag
1081 gcctgagcgt ccagaaatgg tgctcaccat gctccagct aacaggctca gaaaaccagc
1141 ttgcgaataa cagtcctcgt ggccatccct gtgagggtga cgttagcatt accccaacc
1201 tcattttagt tgcctaagea ttgctggcc ttctgtcta gtctctctg taagccaaag
1261 aaatgaacat tccaaggagt tggaagtga gtctatgat tgaacactt gcctcctgt
1321 gtactgtctc ataaacagat gaataaactg aattgtact tt

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AF531293 Histone H2b, member R

1 aagagcgagt cttggcctta gcgcgggctt tgcctccctg cttgccacgt ccagacatag
61 cgagcgcaac tcactacgag caaccacaaa gtgaacggga aaggcggcgc ttttataaa
121 cactattggg cgcgaaaaag aagacgtgtt gttggtagg gctgcagttt aattcaacc
181 aatagtagtg cgtcttctgg atttgcgaat cctgattggg cagacctgac ctctgacgtt
241 accctgaata actaccaatc agacacaaga cttcaactct tcaccttatt tgcataagcg
301 attctatata aaagcgccct gtcataccct gctcacgctg ttttccttt tcgttggcgc
361 tttatagcta cacagtgcta tgccagagcc agcgaagtct gctcccggcc cgaaaaaggg
421 ctccaagaag gcggtgacta aggcgcagaa gaaagacggc aagaagcgca agcgcagccg
481 caaggagagc tattccatct atgtgtacaa ggttctgaag cagggtccacc ctgacaccgg
541 catttcgtcc aaggccatgg gcatcatgaa ttcgtttgtg aacgacattt tcgagcgcat
601 cgcaggtgag gcttcccgcc tggcgcatta caacaagcgc tcgaccatca cctccaggga
661 gatccagacg gccgtgcgcc tgctgctgcc tggggagttg gccaaagcacg ccgtgtccga
721 gggactaag gccgtcacca agtacaccag cgctaagtaa acagtgagtt ggttgcaaac
781 tctcaacct aacggctctt ttaagagcca ccatgttct caaagaaaga gctggtgctt
841 gtattcctcc tctgtggcc actgacaaac cttgtaact tgctactgtg tttttggtc
901 tgaagtagag cagttattta actaatcctt agtgactttt ttttttga tctgccattc
961 taatcttaga gtaagtaag gagatgggaa attttctatt ataagttcga aaccaattaa
1021 aatacgtag aaaccaatta aaatactcgt cggcccccg tcggttagtg atttgaaca
1081 gtgccaagtt gcagcgggtg tcagtttgaa tttgccggg caacgcccgc ccttct

Figure 24. (Page 18 of 46)**NM 001657 Homo Sapiens amphiregulin**

```
1 agacgttcgc acacctgggt gccagcggcc cagaggtccc gggacagccc gaggcgccgc
61 gcccggccgc ccgagctccc caagccttcg agagcggcgc aactcccggt tctccactcg
121 ctcttccaac acccgctcgt ttggcggca gtcgtgtcc cagagaccga gttgccccag
181 agaccgagac gccgccgtg cgaaggacca atgagagccc cgctgctacc gccggcgccg
241 gtggtgctgt cgctcttgat actcggtca gccattatg ctgctggatt ggacctcaat
301 gacacctact ctgggaagcg tgaaccattt tctggggacc acagtgtga tggattgag
361 gttacctcaa gaagtgaat gtcttcaggg agtgagattt cccctgtgag tgaatgcct
421 tctagtagtg aaccgtcctc gggagccgac tatgactact cagaagagta tgataacgaa
481 ccacaaatac ctggctatat tctgatgat tcagtcagag ttgaacaggt agttaagccc
541 ccccaaaaca agacggaaaag tgaaaatact tcagataaac caaaagaaa gaaaaaggga
601 ggcaaaaatg gaaaaaatag aagaacaga aagaagaaaa atccatgtaa tgcagaattt
661 caaaatttct gattcacgg agaatgcaa tatatagagc acctggaagc agtaacatgc
721 aaatgtcagc aagaatattt cgtgaacgg tgtggggaaa agtccatgaa aactcacagc
781 atgattgaca gtatgttacc aaaaattgca ttagcagcca tagctgcctt tatgtctgct
841 gtgatcctca cagctgttgc tgtattaca gtccagctta gaagacaata cgtcaggaaa
901 tatgaaggag aagctgagga acgaaagaaa ctcgacaag agaattgaaa tgtacatgct
961 atagcataac tgaagataaa attacaggat atcacattgg agtcactgcc aagtcatagc
1021 cataaatgat gagtcgggcc tcttccagt ggatcataag acaatggacc cttttgtta
1081 tgatggtttt aaactttcaa ttgtcattt ttatgctatt tctgtatata aaggtgcacg
1141 aaggtaaaaa gtatttttc aagttgtaa taatttattt aatatttaat ggaagtgtat
1201 ttattttaca gtcattaaa ctttttaac caaacagaaa aaaaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa
```

Figure 24. (Page 19 of 46)**M90357 Human basic transcription factor 3**

1 ttatgggtaa tgttcttata gacatccaaa ggtcagaaac tattcccatt tgaaaaatat
 61 ctgttgtggt ataatgtgc tgtttcttt cctcttctcc ctgactttag ggaactgtgc
 121 gcagaaagaa gaaggtgggt catagaacag ccacagcaga tgacaaaaaa cttcagttct
 181 ccttaaagaa gtaggggta aacaatatct ctggtattga agaggcaagt atcaaatttt
 241 gtacttttaa aaaacaagat ttggctggga aaagttaacg ttaatgcatt aaatgggttg
 301 ttgggttttt ttaacttag ggacttcaa gtccctaaga tgtgtttcta ccataaatta
 361 ataaatatca gggagctcat taagtctgaa tgctattaga atacatattc cattccaggc
 421 aaaatttcac ctgtgcttac acgtgaaata ctagttagcc agagctagtt taataaaaca
 481 ttgttttta aagagactgg tcagcattgc taatttaaatt tttcttttc ttaatagggtg
 541 aatatgttta caaaccaagg aacagtgtac cactttaaca accctaaagt tcaggcatct
 601 ctggcagcga acactttcac cattacaggc catgctgaga caaagcagct gacagaaatg
 661 ctaccagca tctaaacca gcttgggtgcg gatagtctga ctagttaag gagactggcc
 721 gaagctctgc ccaacaatg tgagtctct agtaattggt ttaccaggga attactcatt
 781 tagcagctga ttctgatct cagggtcag aatggatatg agtattttta agtttgga
 841 tgcaagcttt aaaaataaca gatttgaac tgattttaag caactgtcct tgctcaagtt
 901 tgcagtaatt gatgtagcgt gccatgattg ttacacttga tttgttgga tgtttctac
 961 ttacttgatt tggatcagat acttttatta actagaaatg atgaaatgt taatttggtg
 1021 ctttgcctaat aactacttgt aagtttgga ttgaaaaaa aattagtgt aattatgaa
 1081 ttacttcagt ttcatctata tagttcgtat taccagtaatt ctttaaaaaa tggcttgcca
 1141 gtattctggc attttaatta cagtgtgata gggatttatt cggggcagaa aatagttag
 1201 ctgaatatac atctgaggat ttggcaggtg tatgctgttt tctgtgctta aaatttgaa
 1261 gaataggaat gcaggaggaa gtcagaggct tatatatggc tcttagtta ccatgtttt
 1321 tctaggtatt gacttaactt gcccaattt tcattttat tatcattg agttgcaggt
 1381 tctaaactgt cagggtcttc agagctgaaa taggcttttg aagtatccca ctgatgcctg
 1441 tatgggccta gtacataact ctctgtgta cgttcattt cttgtgtgat aaaggagagt
 1501 ggatgcttac cactcacaga ctcttaatt ttttacttt aactttttc atttcagtaa
 1561 gtggtgttg agcatcacc ttatgccaca cacagagtag ttgagaaat ggcattctca
 1621 tttgtctccc aaaatctcac catgatttgg tatgtgggtt ttacctgcac tctaaagatt
 1681 ccctactgcc cttatactac ctgaggccta tgggtggccag aggattgaaa gattggtatg
 1741 gaatttgtt gttggcgttc ctagtattt aacctattg tagacattag aatatcatgt
 1801 tattgatagt atcataggat aaaatccca atgtcccta tcatggaat aagtgtaac
 1861 aacacttggc atttcactg ttctttttt tttttttt tttttttg tgaatttta
 1921 ttaaaaacct agacaaataa tgtttacatt ttctttcat agctgtggat ggaaaagcac
 1981 cactgtctac tggagaggat gatgatgat aagttccagg taggaacgtt tgctgtggt
 2041 taacctagag aatcttagcc aaggagaaat aagaaatctt ttaggaaaa actaccagg
 2101 gaagaggggt ggtaagttaa gatggacata gatcttactt agaagagaa aaataatgca
 2161 gtattagga attgagaatt atgtttatag acttgacttg gctgtttct gtttgggatc
 2221 ccaaggatgt gtaggtatct aacctaaat attgaataaa taagtatata tatatgtac
 2281 cctaaatata actattacct gcagagcact aatgacctt gctccctact ttgaaactca
 2341 tgaatttaca agaaggtgtg gattgttca ggtatcttgg gatatatata tgcattctaa
 2401 aatcttagc agcataactc ctttgggaa tcagaggatt ttgtctctta cctgttattg
 2461 gataaattta cgttcttcta aaatatttat tgggcaggag aatcactgga ctcataaata
 2521 ttccacttt gcatagacag gtatccctag gaatcaggaa aattttaaca ttgtgtgta
 2581 ttgtattctt tggttctgct cccccactat tgaccaatgt agagatggga agaggggggc
 2641 attttttct cttttttt tttttgcatt ctgttcttg gggctatgac acagtattta
 2701 tcatcattgg caaatgaatg ctctttcct catcccttt taatatctga taattattg
 2761 tagattggt ttttaagaa ttctactct tttctttc ctatgcttg tggagaattt

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2821 tgatgaggct tccaagaatg aggcaaactg aattgagtca acttctgaag ataaaacctg
2881 aagaagtta ctgggagctg ctattttata ttatgactgc ttttaagaa aattttgtt
2941 tatggatctg ataaaatcta gatctcta attttaagc ccaagcccct tggacactgc
3001 agctctttc agttttgct tatacacaat tcattcttg cagctaatta agccgaagaa
3061 gcctgggaat caagtttgaa acaaagatta ataaagttct ttgcctagt atacagttt
3121 attttttat ttattgacac cgatctgtac acagtaaaaa aaattgctta tagaaagcta
3181 atcatggcat gtaatatggc tgataacctt tggaatttga ttaaagattt aaaatcacgg
3241 tgtaagtgt acaaagggtg tataaagttc tcaggtttga aaactttgtc tccaacagtc
3301 cttagtctt ccatgattta tatggtgggt gtaaatatga gaatagagta ttcttagtg
3361 gataaacaga catttctccc tgatattctc tattgtaagc atatgttaag tgcctttat
3421 gaattaccct cgggtgtatc ttctttatt cctcaatttg tgaagaacta atagctccat
3481 ttgtagatg taacctgagg tttagaactt ctaaaaagta aaagtaactt ccagatccct
3541 tcttttagg atattttata aggtgacttg gaaaaggtag tgtttagaat aggagtggct
3601 cctgggtcat tgcctttcc ttaagtgtaa cacctaata atgaataggg ttatgtttt
3661 atttaataaa aaatatacag taaaattgag catatacagt taaaagaatt tataatgtct
3721 gccactataa ccaggcttac cagacagttt catggtccag aaaatcccta aacatagggt
3781 tacttttaa cattttacaa attacaatga aacaattgtg taatctgaac caaggccatt
3841 tgaggagaaa tagttctact tgatgggtat ttattttaa attttcata gcaatttgca
3901 agtacctttt gaaagtatta tcagttgtat ctaaaatgca ctattaaccg tgg

Figure 24. (Page 21 of 46)**NM 006219 Homo sapiens phosphoinositide-3-kinase, p110 subunit**

1 atgtgcttca gtttcataat gcctcctgct atggcagaca tccttgacat ctgggcggtg
 61 gattcacaga tagcatctga tggctccata cctgtggatt tcctttgcc cactgggatt
 121 tatatccagt tggaggtacc tcgggaagct accatttctt atattaagca gatgttatgg
 181 aagcaagttc acaattaccc aatgttcaac ctcttatgg atattgactc ctatatgtt
 241 gcatgtgtga atcagactgc tgtatatgag gagcttgaag atgaaacacg aagactctgt
 301 gatgtcagac ctttcttcc agttctcaa ttagtgacaa gaagttgtga ccaggggaa
 361 aaattagact caaaaattgg agtccttata ggaaaaggtc tgcattgaatt tgattccttg
 421 aaggatcctg aagtaaatga atttgaaga aaaatgcgca aattcagcga ggaaaaaatc
 481 ctgtcacttg tgggattgtc ttggatggac tggctaaaac aaacatatcc accagagcat
 541 gaaccatcca tccctgaaaa cttagaagat aaactttatg ggggaaagct catcgtagct
 601 gttcattttg aaaactgccca ggacgtgtt agcttcaag tgtctcctaa tatgaatcct
 661 atcaaagtaa atgaattggc aatccaaaaa cgtttgacta ttcattgggaa ggaagatgaa
 721 gttagccct atgattatgt gttgcaagtc agcgggagag tagaatatgt tttgtgtat
 781 catccactaa ttcagttcca gtatatccgg aactgtgtga tgaacagagc cctgccccat
 841 ttatacttg tggaatgtcg caagatcaag aaaatgtatg aacaagaaat gattgccata
 901 gaggtgcga taaatcgaat tcatctaat ctctcttc cattaccacc aaagaaaaca
 961 cgaattatt ctcatgttg ggaaaataac aacccttcc aaattgtctt ggtaaggga
 1021 aataaactta acacagagga aactgtaaaa gttcatgtca gggctggtct tttcatggt
 1081 actgagctcc tgtgtaaaac catcgtaagc tcagaggat cagggaaaaa tgatcatatt
 1141 tggatgaac cactggaatt tgatattaat atttgact taccaagaat ggctcgatta
 1201 tgtttgctg ttatgcagt ttggataaa gtaaaaacga agaaatcaac gaaaactatt
 1261 aatccctcta aatatcagac catcaggaaa gctggaaaag tgcattatcc ttagcgtgg
 1321 gtaaatcga tggttttga ctttaaagga caattgagaa ctggagacat aatattacac
 1381 agctggtctt catttctga tgaactgaa gaaatgtga atccaatggg aactgtcaa
 1441 acaaatccat atactgaaaa tgcaacagct ttgcatgta aatttccaga gaataaaaaa
 1501 caaccttatt attacctcc ctgcgataag attattgaa aggcagctga gattgcaagc
 1561 agtgatagtg ctaatgtgtc aagtcgaggt ggaaaaaagt ttctcctgt attgaaagaa
 1621 atcttggaac gggatccctt gtctcaactg tgtgaaatg aaatggatct tatttgact
 1681 ttgcgacaag actgccgaga gattttcca caatcactgc caaattact gctgtcaatc
 1741 aagtggaaata aacttgagga tgtgtctcag ctccagcgc tcttcagat ttggcctaaa
 1801 ctgccccccc gggaggccct agagcttctg gatttcaact atccagacca gtacgttga
 1861 gaatatgtg taggctgcct gcgacagatg agtgaatga aactttctca atattctta
 1921 caactggtgc aagtgttaaa atatgagcct ttcttgatt gtgccctctc tagattccta
 1981 ttgaaaagag cacttggtaa tcggaggata gggcagttc tattttgga tcttaggtca
 2041 gaagtgcaca ttctgctgt ctactgacaa ttggtgtca tcctgaagc atactccgg
 2101 ggaagtgtgg ggcacatgaa agtgccttct aagcaggttg aagcactcaa taagttaaaa
 2161 actttaataa gtttaataa actgaatgcc gtgaagttaa acagagccaa agggaaggag
 2221 gccatgcata cctgtttaa acagagtgtc taccgggaag cctctctga cctgcagtca
 2281 cccctgaacc catgtgttat ccttcagaa ctctatgttg aaaagtgcaa atacatggat
 2341 tccaaaatga agccttttg gctgtgtatc aataacaagg tatttggtga ggattcagtt
 2401 ggagtgtatt taaaaatgg tgatgattt cgacaggata tgttgacact ccaaatgttg
 2461 cgcttgatgg atttactctg gaaagaagct ggttggatc ttggatgtt gccttatggc
 2521 tgtttagcaa caggagatcg ctctggcctc attgaagtg tgagcacctc tgaacaatt
 2581 gctgacattc agctgaacag tagcaatgtg gctgtcgag cagccttcaa caaagatgcc
 2641 ctctgaact ggcttaaga atacaactct ggggatgacc tggaccgagc cattgaggaa
 2701 ttacactgt cctgtgctg ctactgtga gcttctatg tcctgggat tggtagacaga

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2761 catagtgaca acatcatggt caaaaaaact ggccagctct tccacattga ctttgacat
2821 attcttgga atttcaaate taagtttggc attaaaagg agcgagtgcc tttattctt
2881 acctatgatt tcatccatgt cattcaacaa ggaaaaacag gaaatacaga aaagtttggc
2941 cggttccgcc agtgttgtga ggatgcatat ctgattttac gacggcatgg gaatctctc
3001 atcactctct ttgcgctgat gttgactgca gggcttctg aactcacatc agtcaaagat
3061 atacagtatc ttaaggactc tctgcatta gggaagagtg aagaagaagc actcaaacag
3121 ttaagcaaa aatttgatga ggcgctcagg gaaagctgga ctactaaagt gaactggatg
3181 gccacacag tcggaaaga ctacagatct taa

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X04412 Human Gelsolin

1 gccgtgtcgc caccatggct ccgcaccgcc ccgcgcccgc gctgctttgc gcgctgtccc
 61 tggcgtgtgt cgcgtgtcgc ctgcccgtcc gcgcggccac tgcgtcgcgg ggggcgtccc
 121 aggcgggggc gcccagggg cggtgcccgc aggcgcggcc caacagcatg gtggtggaac
 181 accccgagtt cctcaaggca gggaaggagc ctggcctgca gatctggcgt gtggagaagt
 241 tcgatctggt gcccggtccc accaaccttt atggagactt cttcacgggc gacgcctacg
 301 tcactctgaa gacagtgcag ctgaggaacg gaaatctgca gtatgacctc cactactggc
 361 tgggcaatga gtgcagccag gatgagagcg gggcgccgc catcttacc gtgcagtgg
 421 atgactacct gaacggccgc gccgtgcagc accgtgaggt ccagggttc gagtcggcca
 481 cttctctagg ctactcaag tctggcctga agtacaagaa aggaggtgtg gcatcaggat
 541 tcaagcacgt ggtaccaac gaggtggtgg tgcaagact cttccaggtc aaagggcggc
 601 gtgtggtccg tgccaccgag gtacctgtgt cctgggagag ctcaacaat ggcgactgct
 661 tcactctgga cctgggcaac aacatccacc agtggtgtgg ttccaacagc aatcggtatg
 721 aaagactgaa ggccacacag gtgtccaagg gcatccggga caacgagcgg agtgccggg
 781 cccgagtga cgtgtctgag gagggcactg agcccgaggc gatgtccag gtgctgggccc
 841 ccaagccggc tctgctgca ggtaccgagg acaccgcaa ggaggatgcg gccaacgca
 901 agctggccaa gctctacaag gtctcaatg gtgcagggac catgtccgc tccctctgg
 961 ctgatgagaa cccctcgcc cagggggccc tgaagtcaga ggactgcttc atcctggacc
 1021 acggcaaaaga tgggaaaatc ttgtctgga aaggcaagca ggcaaacacg gaggagagga
 1081 aggtgccct caaacagcc tctgacttca tcaccaagat ggactacccc aagcagactc
 1141 aggtctcggc cttctctgag ggcggtgaga cccactgtt caagcagttc ttcaagaact
 1201 ggcgggaccc agaccagaca gatggcctgg gcttgccta ccttccagc catatcgcca
 1261 acgtggagcg ggtgcccttc gacgccgcca cctgcacac ctccactgcc atggccgccc
 1321 agcacggcat ggatgacgat ggcacaggcc agaaacagat ctggagaatc gaaggttcca
 1381 acaagtgccc cgtggaccct gccacatatg gacagtctta tggaggcgac agctacatca
 1441 ttctgtacaa ctaccgccat ggtggccgcc aggggcagat aatctataac tggcagggtg
 1501 cccagtctac ccaggatgag gtcgtgcat ctgccatct gactgctcag ctggatgagg
 1561 agctgggagg taccctgtc cagagccgtg tggccaagg caaggagccc gccaccta
 1621 tgagcctgtt tggagggaag cccatgatca tctacaagg cggcacctcc cgcgaggcg
 1681 ggcagacagc cctgccagc acccgctct tccaggtccg cgccaacagc gctggagcca
 1741 cccgggctgt tgaggtattg cctaaggctg gtgactgaa ctccaacgat gcctttgtc
 1801 tgaaaacccc ctacgcgcc tacctgtggg tgggtacagg agccagcgag gcagagaaga
 1861 cgggggcccc gagctgtctc aggtgtctgc gggcccaacc tgtgcagggt gcagaaggca
 1921 gcgagccaga tggcttctgg gaggccctgg gcgggaaggc tgcctaccgc acatccccc
 1981 ggctgaagga caagaagatg gatgccatc ctctcgctt cttgctgc tccaacaaga
 2041 ttggacgttt tgtatcgaa gaggttctg gtgagctcat gcaggaagac ctggcaacgg
 2101 atgacgtcat gcttctggac acctgggacc aggtcttct ctgggttga aaggattctc
 2161 aagaagaaga aaagacagaa gccttgactt ctgctaagcg gtacatcgag acggaccag
 2221 ccaatcgga tggcggagc ccatcaccg tggtaagca aggtttgag cctccctct
 2281 ttgtggctg gttccttggc tgggatgatg attactggtc tgtggacccc ttggacaggg
 2341 ccatggctga gctggctgcc tgaggagggg cagggccac ccatgtcacc ggtcagtgcc
 2401 ttttgaact gtcctccct caaagaggcc ttagagcgag cagagcagct ctgctatgag
 2461 tgtgtgtgtg tgtgtgtgt gttctttt ttttttta cagtatcaa aaatagccct
 2521 gcaaaaattc agatccttg caaaattgtc taaaatgtca gtgtttgga aattaaatcc
 2581 aataaaaaca tttgaagtg tg

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NM 001759 Homo sapiens Cyclin D2

1 agagcgagca ggggagagcg agaccagttt taaggggagg accggtgcga gtgaggcagc
 61 cccgaggctc tgctcgccca ccaccaatc ctgcctccc ttctgtcca cttctctct
 121 ctgccctcac ctctccccg aaaacccct atttagccaa aggaaggagg tcaggggaac
 181 gtctcccct cccttccaa aaaacaaaa cagaaaaacc ctttccagg ccggggaaag
 241 caggagggag agggggcggc gggctggcca tggagctgct gtgccacgag gtggacccgg
 301 tccgcagggc cgtgcgggac cgcaacctgc tccgagacga ccgctcctg cagaacctgc
 361 tcaccatcga ggagcgtac ctccgcagt gctctactt caagtgcgtg cagaaggaca
 421 tccaacctca catgcgcaga atggtggcca cctggatgct ggaggtctgt gaggaacaga
 481 agtgcaaga agaggtcttc cctctggcca tgaattacct ggaccgttc ttggctgggg
 541 tcccactcc gaagtcccat ctgcaactcc tgggtgctgt ctgcatgtc ctggcctcca
 601 aactcaaaga gaccagccc ctgaccggc agaagctgt catttacacc gacaactcca
 661 tcaagcctca ggagctgctg gagggggaac tgggtggtct ggggaagtgt aagtgggaac
 721 tggcagctgt cactcctcat gacttcatt agcacatct gcgcaagctg cccagcagc
 781 gggagaagct gtctctgac cgcaagcat ctcagacct cattgctctg tgtgccaccg
 841 actttaagt tgccatgtac ccaccgtca tgcgcgaac tggaaagtgt ggagcagcca
 901 tctgtgggt ccagcaggat gaggaagtga gctcgtcac ttgtgatgcc ctgactgagc
 961 tgctggctaa gatcaccaac acagacgtg attgtctcaa agcttgccag gagcagattg
 1021 aggcggtgct cctcaatagc ctgcagcagt accgtcagga ccaacgtgac ggateccaagt
 1081 cggaggatga actggaccaa gccagcacc ctacagacgt gcgggatac gacctgtgag
 1141 gatgccagtt gggccgaaag agagagacgc gtccataatc tggctcttc tttttctgg
 1201 ttgttttgt tcttctgtt ttagggtgaa acttaaaaa aaaattctgc cccacctag
 1261 atcatatta aagatcttt agaagtgaga gaaaaaggc ctacgaaac ggaataataa
 1321 aaagcatttg gtgcctatt gaagtacagc ataagggaat ccctgtata tgcgaacgt
 1381 tattgttga ttatgtaaaa gtaatagtaa aatgcttaca ggaaaacctg cagagtagtt
 1441 agagaatatg tatgctgca atatgggaac aaattagagg agacttttt tttcatgtt
 1501 atgagctagc acatacccc cctttagta taattcaag gaactgtgta cgccattat
 1561 ggcattgatta gattgcaaag caatgaactc aagaaggaa tgaataagg agggacatga
 1621 tggggaagga gtacaaaaca atctcaac atgattgaac cattgggat ggagaagcac
 1681 ctttgcctc agccacctg tactaagta ggagtgtagt tggatctcta cattaatgtc
 1741 ctctgtctg ctacagtagc tctaccta aaaaagatgt ttattttgc cagttggaca
 1801 caggtgattg gctcctgggt tcatgttct gtgacatct gcttctctt ccaaatgcag
 1861 ttcatgtag acaccacct attgctatc aatggggaaa ttagctatg ggccataacc
 1921 aaaactcaca tgaacaggag gcagatggag accaagggtg ggateccaga tggagtctt
 1981 tctgtattg tatttaaaag ggtaattgt ccttggcatt tctcttaga aaaaaactaa
 2041 ttttgggtgc tgattggcat gtctggttca cagtttagca ttgtataaa ccattccatt
 2101 cgaaaagcac ttgaaaaat tgttcccgag cgatagatgg gatggttat gcaagtcag
 2161 ctgaatactc ctccctctt ctctttgcc cctcccttc ctgccccag tctgggttac
 2221 tcttgcctc tggatctgg cgttcttgg tacacagttc tgggttct accaggactc
 2281 aagagacacc cctcctgct gacattcca tcacaacatt cctcagacaa gcctgtaaac
 2341 taaaatctgt taccattctg atggcacaga aggatcttaa ttccatctc tatactctc
 2401 ctttggacat ggaaagaaaa gtattgctg gtgcaaagat agatggctga acatcagggt
 2461 gtggcatttt gtccctttt ccgtttttt tttttatt gtgtgtta atttattgc
 2521 aaagttgat tcagcgtact tgaattttc ttctctcca ctcttagag gcattcagtt
 2581 agcaaagggt ttggagcaac aactttttt tttttttg cacaattgta attgacaggt
 2641 aatgaagcta ttgttaaaa tattgcctt ttaagtaaa aaagaaaaat cagaacaggg
 2701 ctatttgaag aattatttta tacacagatt ctgcctgtt tcatagtat aggggtgaag
 2761 acggaaaaca atctaagggt ctctatttt ttaattttg tttgttcag tttgtttt

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2821 tttttttt gcgctgctaa gaagctaaag tcacccatcc ttattcacgt tgacagtacc
2881 tagctgtaat gtttcacaga gtgtgctgct atttataaa cattttata atatattatt
2941 ttactgttta aattccaagt cctgaagtag atggttgaga tatgagttct tcgtactgga
3001 aaagcccttc cgtagtttgt ttctcttg tagcataatc atggttggtt ttttttct
3061 ttttgggtt ttgggtttt ttttttct ctgatcacat tctcaaaga cggagtattc
3121 ttacctcag gtttactgga caaaatcaat aactacaaa ggcaatgatt cacgctttt
3181 tttcataat acctacaaac cgtacagtt ctgcttgga gccattcgc atgaggaata
3241 cagaagcagt gtgagcagg ctagctccct ctcagggtga aggcaggcgc gtctcactcc
3301 caggacctt ttggctatg gaggccatgc ggctccagt tagaccctgg tatcctcatc
3361 atgatggaaa aaatacattg aaccaaggga tctcctcc ccttcaaggc agacgttcag
3421 tacaacatt tatcggttag gctcagatgt cgtaatgtc acttaggtac cagggttcag
3481 gaaacagact aaaaagaatt ccaccaggct gtttgagat cctcatctg gagcttttc
3541 aaaagcggg cttcatctgc aaaggccct tcatctga agttttccc ctccgtctt
3601 cccctccct ggcatggaca cttgtgtt aggatcatct ctcagggtt ctaggtctg
3661 aatctgcgag tagatgaacc tgcagcaagc agcgtttatg gtgcttcct ctccctctc
3721 tgtctcaaac tgcgcaggca agcactatgc aagcccaggc cctctgctga gcggtactaa
3781 acggtcgggt ttcaatcac actgaattgg caggataaga aaaataggtc agataagtat
3841 gggatgatag tgaaggag gtgaaggagc tgcctctca cagaggtaa attccagatg
3901 agtcagtctc ttgggaagtg ttttagaag ggttcaggac ttgtgagtt agcatgacc
3961 taaaattcta ggggatttct ggtgggacaa tgggtggga atttgaagt ttggagagg
4021 gaagtggagc agccagcaag taagtagcc agagtttct caagagccag cttgtcag
4081 cacactctcc tgggccccaa ggagtcac ggaatggga aagtgggaac cttggagttc
4141 ttgggaatct tggagcctaa agagaaccg aggtgcaaat tcattcatg gtgactgacc
4201 cttgagctta aacagaagca gcaaatgaaa gaaccggaca aataaggaag ggcacaagcc
4261 taccgactc tattacagt ctgtaactt ccactctcc ttagtccc aggccctgg
4321 gtcttctag cttttctt tccatcctt ggggcctgt gtgatgatg gtgtggggt
4381 gccgatggga aagtcggggg ttgttaggt ttctgctg ctctgctta aacacaagaa
4441 ggaatcctgg atttgccct ctcttagct cttagctct ttgtaggag tttgtcca
4501 gaggagctct ccccttga tttgaactg ctctttgt ttgtgtgt cttctctc
4561 ttttctac ctccactaa aggggtcca aattatctg gtctttct acctgtgt
4621 gtttctat ctctttact tccatctgt ttgttttc tccatcagt ggggccgagt
4681 tgtccccc gctgcccc tttgatct tccctctt tggccaaac ctaggggga
4741 gaaatcctag tatccaaaa atatagcta agcataatta aactccatgc ggtccataa
4801 cagccaagaa gcctgcagga gaaagccaag ggcagttcc tccgagaac acccatgcg
4861 tgctgagagg cgagctcct gaagaagggg ctgttctcc aggaggcct atttgaact
4921 gcctcaggac cccactggag agcacagcat gccttactac tgggtcatcc ttggtctatg
4981 tgctctgac tggaggtct gttctgctc ttatagcca ggtcaggggc acacatggct
5041 taagtgaaca agccagagga gaagacaacc ctgacagcat cacgtgcat ccattgcta
5101 gcaggattgg caactctca gacggagctg cgttccctg cagtctagca cctctaggc
5161 ctctccagac tgtgccttg gagctctgg actgaaagt taagaacata aggcaggatc
5221 agatgactct ctcaaagg gcagggaat ttctctcca tgggccacag gggacagggc
5281 tgggagaaga aatagactg caccatgt catgtaaata attgatttc tagtcaaga
5341 agataatatt ggtagtgtg gaattggagg taggaagggg aggaagtct agtaagccag
5401 ttggttcta agccaaaagg attcctctt gttatctct gagacagtc aacctgaga
5461 atagcttaa agggaaatt aatgctgaga tgataaagc ccttaagcc acaaacct
5521 ctgtagctat agaattagtg caggtttcta ttggttgga ctcagagcaa ttacaagag
5581 ctgttcatgc agccatccat ttgtcaaaa taggtaaga agattcaaga ggtatttat
5641 tacttctca taccatagg cttttagta ttctggatc taaacaacc agaattgtca
5701 ttacggcac aacgatacta cttctgtgtg tgtctgtt taaactggc tggctatca

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5761 gaccctattc tcggctcagg tttagagaag ccatcagcaa atgtgtacgt gcatgctgta
5821 gctgcagcct gcatcccttc gcctgcagcc tactttgggg aaataaagtg ccttactgac
5881 ttagccatt acagtatcca atgtctttg acaggtgcct gtcctgaaa aacaaagttt
5941 ctatttttat ttttaattgg ttagttctt aactgctggc caactcttac atccccagca
6001 aatcatcggg ccattggatt tttccatta tttcatcac cttatatca tgtacctcag
6061 atctctctct ctctctctc tctcagttat atagtttctt gtcttggaact ttttttct
6121 tttcttttc tttttttt tgcttaaaa caagtgtgat gccatatcaa gtccatgta
6181 ttcttcaca gtgtactcta taagagggtg ggggtgtctg ttggtcagga tgtagaaag
6241 tgctgataag tagcatgac agtgtatgcg aaaagggttt taggaagtat ggcaaaaatg
6301 ttgtattggc tatgatggtg acatgatata gtcagctgcc ttttaagagg tcttatctgt
6361 tcagtgttaa gtgattfaaa aaaataataa cctgttttct gactagttta aagatggatt
6421 tgaanaatggt ttgaatgca attagggtat gctatttga caataaactc acctgacct

Figure 24. (Page 27 of 46)**NM 004444 Ephrin Receptor (EphB4)**

1 cgtccacccg cccagggaga gtcagacctg ggggggag gagcccccaa actcagttcg
 61 gatctaccc gagtgaggcg gcgccatgga gtcgcgggtg ctgctctgct gggcttcgtt
 121 ggccgcagct ttggaagaga ccctgctgaa cacaaaattg gaaactgctg atctgaagtg
 181 ggtgacattc ctcaggttg acgggcagtg ggaggaactg agcggcctgg atgaggaaca
 241 gcacagcgtg cgcacctacg aagtgtgtga agtcagcgt gccccgggccc agggccactg
 301 gcttcgcaca ggttggttcc cacggcgggg cgccgtccac gtgtacgcca cgtgcgctt
 361 caccatgctc gaggtcctgt cctgcctcg ggctgggccc tctgcaagg agaccttcac
 421 cgtctctac tatgagagcg atgcggacac ggccacggcc ctcacgccag cctggatgga
 481 gaaccctac atcaagggtg acacgggtgg cgcgaggcat ctcacccgga agcgcctgg
 541 ggccgaggcc accgggaagg tgaatgtcaa gacgtgctg ctgggaccgc tcagcaaggc
 601 tggtctctac ctggccttc aggaccaggg tgctgcatg gccctgctat cctgcacct
 661 ctctacaaa aagtgcgccc agctgactgt gaacctgact cgattcccgg agactgtgcc
 721 tcgggagctg gttgtgcccg tggccggtag ctgctgggtg gatgccgtcc ccgccctgg
 781 cccagcccc agcctctact gccgtgagga tggccagtgg gccgaacagc cggtcacggg
 841 ctgcagctgt gtcgggggt tcgaggcagc tgaggggaac accaagtcc gagcctgtgc
 901 ccagggcacc tcaagcccc tgtaggaga agggctctgc cagccatgcc cagccaatag
 961 cactctaac accattgat cagccgtctg ccagtgccgc gtcgggtact tccgggcacg
 1021 cacagacccc cggggtgcac cctgcaccac cctccttcg gtcgcggga gcgtggttc
 1081 ccgcctgaac ggctcctccc tgcacctgga atggagtgc ccctggagt ctggtggccg
 1141 agaggacctc acctacgccc tccgtgcgg ggagtgcga cccggaggct cctgtgcgc
 1201 ctgcggggga gacctgactt ttgaccccgg ccccgaggac ctggtggagc cctgggtgtg
 1261 ggttcgaggg ctactgccg acttcaccta taccttgag gtcactgcat tgaacgggtg
 1321 atctcctta gccacggggc cgtccatt tgagcctgtc aatgtacca ctgaccgaga
 1381 ggtacctcct gcagtgtctg acatccgggt gacgcggtcc tcaccagca gcttgacct
 1441 ggctgggct gttccccgg caccagtgg gccgtggctg gactacgagg tcaataacca
 1501 tgagaagggc gccgagggtc ccagcagcgt gcggttctg aagacgtcag aaaaccgggc
 1561 agagctgcgg gggctgaagc ggggagccag ctacctggtg caggtaggg cgcgtctga
 1621 ggccggctac gggcccttcg gccaggaaca tcacagccag accaactgg atgagagcga
 1681 gggctggcgg gacagctgg cctgattgc gggcacggca gtcgtgggtg tggctctgt
 1741 cctggtgtc attgtgtc cagtctctg ctcaggaag cagagcaatg ggagagaagc
 1801 agaattatcg gacaaacag gacagtatc catcgacat ggtactaagg tctacatga
 1861 ccccttact tatgaagacc ctaatgagc tgtgaggga ttgcaaaag agatcgatg
 1921 ctctacgtc aagattgaag aggtgattgg tgcaggtgag ttggcgagg tgtccgggg
 1981 gcggctcaag gccccaggga agaaggagag ctgtgtggca atcaagacc tgaagggtg
 2041 ctacacggag cggcagcggc gtgagttct gagcaggcc tccatcatgg gccagttga
 2101 gaccccaat atcatccgc tggaggcgt ggtaccaac agcatgccc tcatgattt
 2161 cacagagttc atggagaac gcgcctgga ctcttctc cggctaaac aggcagatt
 2221 cacagtcac cagctcgtg gcagctgcg ggcatcgcc tcgggcatgc ggtacctgc
 2281 cgagatgagc tacgtccac gagacctggc tgctcgcaac atcctagtca acagcaacct
 2341 cgtctgcaaa gtgtctgact ttggccttc cgattctc gaggagaact ctccgatcc
 2401 cacctacag agtcctctg gaggaaagat tccatccga tggactgccc cggaggccat
 2461 tgcttccgg aagttcact ccgccagtga tgctggagt tacgggattg tgatgtgga
 2521 ggtgatgtca ttggggaga ggccgtact ggacatgagc aatcaggacg tgatcaatgc
 2581 cattgaacag gactaccggc tgccccgcc ccagactgt cccacctccc tccaccagct
 2641 catgctggac tgtggcaga aagaccgga tgccggccc cgttcccc aggtgtcag
 2701 cgccctggac aagatgatcc ggaacccgc cagctcaaa atcgtggccc gggagaatg
 2761 cggggcctca caccctccc tggaccagc gcagctcac tactcagctt ttgctctgt

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2821 gggcgagtgg cttcgggcca tcaaatggg aagatacgaa gaaagtctg cagccgctgg
2881 ctttggctcc ttcgagctgg tcagccagat ctctgctgag gacctgctcc gaatcggagt
2941 cactctggcg ggacaccaga agaaaatctt ggccagtgtc cagcacatga agtcccaggc
3001 caagccggga accccgggtg ggacaggagg accggcccc cagtactgac ctgcaggaac
3061 tccccacccc agggacaccg cctccccatt ttccggggca gagtggggac tcacagaggc
3121 cccagccct gtgccccgt ggattgcact ttgagccgt ggggtgagga gttggcaatt
3181 tggagagaca ggattgggg gttctgcat aataggagg gaaaatcacc cccagccac
3241 ctgggggaac tcagaccaa gggtgagggc gccttccct caggactggg tgtgaccaga
3301 ggaaaaggaa gtgccaaca tctccagcc tcccagggtg cccctcac ctgatgggt
3361 gcgtcccg agacaaaga gagtgtgact ccctgccag ctccagagt ggggggctgt
3421 ccagggggc aagaagggt gtcagggcc agtgacaaa tcattgggt tttagtccc
3481 aactgtgc tgcaccacc aaactcaatc atttttcc ctgtaaatg cccctcccc
3541 agctgctgc tcatattga aggttttga gttttgtt tggcttaat ttttcccc
3601 gtcccttt ttttcttcg tttgtttt ctaccgtcct tgcataact ttgtgtgga
3661 gggaacctgt tcatatgg cctccttgc ccaagtgaa acaggggcc atcatcatgt
3721 ctgttccag aacagtgcct tggcatccc acatccccg accccgcctg ggaccccaa
3781 gctgtgtcct atgaagggt gtgggtgag gtagtga aaa ggcggtagt tgggtgtgga
3841 accagaaac ggacccgt gcttgagg gttctaaat tatattaaa aaagtaact
3901 ttgtataa taaaagaaa tgggacgtg cccagctcca ggggt

Figure 24. (Page 29 of 46)**M18737 Human Hanukah Factor /granzyme A**

1 atgaggaact cctatagatt tctggcatcc tctctctcag ttgtcgttcc tctcctgcta
61 attcctgaag atgtctgtga aaaaattatt ggaggaaatg aagtaactcc tcattcaaga
121 ccctacatgg tctacttag tcttgacaga aaaaccatct gtgctggggc ttgattgca
181 aaagactggg tgttgactgc agctcactgt aacttgaaca aaaggcccca ggtcattctt
241 ggggctcact caataaccag ggaagagcca acaaacaga taatgcttgt taagaaagag
301 ttccctatc catgetatga ccagccaca cgcgaagggtg acctaaact ttacagctg
361 acggaaaaag caaaaattaa caaatatgtg actatccttc atctacctaa aaagggggat
421 gatgtgaaac caggaacat gtgccaagtt gcagggtggg ggaggactca caatagtga
481 tcttggtccg atactctgag agaagtcaat atcaccatca tagacagaaa agtctgcaat
541 gatcgaaatc actataattt taaccctgtg attggaatga atatggttg tgctggaagc
601 ctccgagggtg gaagagactc gtgcaatgga gattctggaa gccctttgtt gtgcgagggt
661 gttttccgag gggtcacttc ctttggcctt gaaaataaat gcggagacc cgtgggcct
721 ggtgtctata ttctctctc aaagaaacac ctcaactgga taattatgac tatcaaggga
781 gcagttaaa taaccgttc ctttcattta ctgtggcttc ttaatcttt caca

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NM 000551 von Hippel-Lindau tumor suppressor (VHL)

1 acgcagctcc gccccgcgtc cgacccgcgg atcccgcggc gtccggcccc ggtggtctgg
 61 atcgcggagg gaatccccc gagggcgagg aactgggacg aggccgaggt aggcgcggag
 121 gaggcaggcg tgaagagta cgcccctgaa gaagacggcg gggaggagtc gggcgccgag
 181 gagtccggcc cggaagagtc cgcccggag gaactgggcg ccgaggagga gatggaggcc
 241 gggcgggccc ggcccgtct gcgtcggtg aactcgcgcg agccctccca ggtcatcttc
 301 tgcaatcgca gtccgcgct cgtgctgccc gtatggctca acttcgacgg cgagccgag
 361 ccctacccaa cgctgccgcc tggcacgggc cgcgcacatc acagctaccg aggtcacctt
 421 tggctcttca gagatgcagg gacacacgat gggcttctgg ttaacaaac tgaattattt
 481 gtgcatctc tcaatgttga cggacagcct attttgcca atatcacact gccagtgtat
 541 actctgaaag agcgatgcct ccagggtgtc cggagcctag tcaagcctga gaattacagg
 601 agactggaca tcgtcaggtc gctctacgaa gatctggaag accacccaaa tgtgcagaaa
 661 gacctggagc ggctgacaca ggagcgcat gcacatcaac ggatgggaga ttgaagattt
 721 ctgttgaaac ttacactgtt tcactcagc tttgatgg actgatgagt ctgatctag
 781 atacaggact ggttccctcc ttagtttcaa agtgtctcat tctcagagta aaataggcac
 841 cattgcttaa aagaaagtta actgacttca ctaggcattg tgatgtttag gggcaaacat
 901 cacaaaatgt aatttaatgc ctgccatta gagaagtatt taccaggaga aggtgggtgc
 961 attttgcct cctagtaagt caggacagct tgtatgtaag gaggtttata taagtaattc
 1021 agtgggaatt gcagcatatc gtttaatttt aagaaggcat tggcatctgc tttaatgga
 1081 tgtataatac atccattcta catccgtagc ggttggtgac ttgtctgctt cctgctttgg
 1141 gaagactgag gcacccgtga ggcagggaca agtctttctc ctcttgaga cccagtgcc
 1201 tgcacatcat gagccttcag tcagggtttg tcagaggaa aaaccagggg acactttgtt
 1261 agaaagtgtc tagagggtct gcctctattt ttgtggggg gtgggagagg ggacctaaa
 1321 atgtgtacag tgaacaaatg tctaaaggg aatcattttt gtaggaagca tttttataa
 1381 tttctaatg cgtgcacttt ctcgggtccac tctgttgaa gtgctgtttt attactgttt
 1441 ctaactagg attgacattc tacagttgtg ataatagcatt tttgtaact tgccatccgc
 1501 acagaaaata cgagaaaatc tgcattgttg attatagat taatggacaa ataagttttt
 1561 gctaaatgtg agtatttctg ttctttttg taaatatgtg acattcctga ttgattggg
 1621 ttttttgtt gttgtgttt ttgtttgtt ttgtttttt ggatggagkc tcactctgt
 1681 caccaggct ggagtgcagt ggcgccatct cggctcactg caacctctgc ctctgagtt
 1741 cagtaatcc tctgagtag ctgggattac aggtgcctgc caccacgctg gccaattttt
 1801 gtacttttag tagagacagt gtttcgcat gttggccagg ctggtttcaa actcctgacc
 1861 tcagggtgat cggccacctc agcctcccaa aatggtggga ttacaggtgt gtgggccacc
 1921 gtgcctggct gattcagcat ttttatcag gcaggaccag gtggacttcc acctccagcc
 1981 tctgtccta ccaatggatt catggagtag cctggactgt ttcatagttt tctaaatgta
 2041 caaattctta taggctagac ttgattcat taactcaaat tcaatgcttc taccagactc
 2101 agtttttgt aactaataga tttttttt cactttgtt ctactcttc ctaatatgct
 2161 ttttaaaaa atctccccag tagagaaaca ttggaaaag acagaaaact aaaaaggaag
 2221 aaaaagatc cctattagat acacttctta aatacaatca cattaacatt ttgagctatt
 2281 tcttccagc ctttttaggg cagattttgg ttggtttta catagttgag attgtactgt
 2341 tcatacagtt ttataccctt ttcatthaa cttataact taaatattgc tctatgttag
 2401 tataagcttt tcacaaacat tagtatagtc tccctttat aattaatgtt tgtgggtatt
 2461 tcttggcatg catctttaat tcttatcct agcctttggg cacaattcct gtgctcaaaa
 2521 atgagagtga cggctggcat ggtggctccc gcctgtaate ccagtacttt gggaagccaa
 2581 ggtaagagga ttgcttgagc ccagaacttc aagatgagcc tgggctcata gtgagaaccc
 2641 gtctatacaa aaaattttta aaaattagca tggcggcaca catctgtaat cctagctact
 2701 tggcaggctg aggtgagaag atcattggag tttaggaatt ggaggcggca gtgagtcagt

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2761 agtatgccgc tgcactccag cctgggggac agagcaagac cctgcctcaa aaaaaaaaaa
2821 aaaaaaaatt caggccggga atggtggttc acgcctgtaa tcccagcact ttggggggtc
2881 gaggtgggca gatcacctga ggtcaggagt tcgagaccag cctggccaac atggtaaac
2941 cccatttcta ctaaaaata caagaattag ctgggtgtgg tggcgcagtc ctgtaacct
3001 agctactcag gaggtgagg caggagaatc acttgacccc aggaggcgaa gattgcagt
3061 agctgatac gcaccattgt actccagcct gtgtgacaga gcaatactct tgtcccaaaa
3121 aaaaaaaaaa ttcaaatcag agtgaagtga atgagacact ccagttttcc ttctactccg
3181 aattttagct cctcctttca acattcaaca aatagtcttt tttttttt tttttttg
3241 gggatggagt ctccctctgt tggccaggct ggagtgcaga ggtgcgatct ctgctcacta
3301 caagctctgc ctcccgagtt caagtgttc tcttggtca cctcctgag ctgggattac
3361 aggcgcctgc caccatgcct ggctaatttt gtgttttag tggagacggg gtttcacat
3421 gttgtccagg atggtctga tctcctgacc ttgtgatcca cccacctcag cctcccaag
3481 tgggtgggatt acaggtgtga gccaccgct ccagccagct ttattttt tttaagctg
3541 tctttgtgc aaaatgatag tcatgtctc tctgttaaa acctgcaggc cgagcacagt
3601 ggctcatgcc tgtaatccca gcattttggg agaccaaggc ggatggatca cctgaggta
3661 ggagctcaag accagcctgg ctaacatggt gaaacctcat ctccactaa aatacaaaaa
3721 ttgccggccg cggcggctca tgcctgtaat ccagcactt tgggaggcct aggcgggtg
3781 atcacgacgt caggaaatcg agaccatcct ggctaacacg ggtgaaacct cgtctctatt
3841 aaaaaataga aaaaattagg cgggcgtggt ggtgagcgcc tgtagtcca gctactcag
3901 agcctgaggc aggagaatgg catgaacctg gaagggtggag ctgacagtga gctgagatg
3961 tgccactgca ctctaacctg ggcgacagag tgagactccg tctcaaaaaa aaaaacaaaa
4021 accaaaactt atccaggtgt ggcggtgggc gcctgtgagg caggcgaatc tctgaacct
4081 gggaggcgga ggttgacagt agccaagatc acaccattgc actccagcct gggaacaag
4141 agtgaaatc catctcaaaa ccaaatttc aaaaaaaaaa catgccgctt gactactgt
4201 ttttggtgt tgtccaagga aaattaaaac ctgtagcatg aataatggtt gtttcattt
4261 cgaatctgt gaatgtatta aatataatgc tcttaagaga cggtagaagt cctatttcaa
4321 gttttttt tttgtttt ttttaagct gtttttaac acattaaatg gtgctgagta
4381 aaggaaatag gcagggtgtg ttgtgtggtg ttttaactag gcgcttctct ctacagagat
4441 ttgaaacct gtttacataa aggcccaaga tgggaaggag atccaaacat aagccaccag
4501 cctcattcca agtctctct cttccaacc ctggattttt ttttttatt taacattgtt
4561 tcttttagct ttattttct tataaaagaa atgtatcact ataaaaaatt acacactaca
4621 gaaaaatatt aagaagaaaa acattcacat cggaaacaaa gttttttccc atgaaaacag
4681 aacccaaaag ggtaagtgt tagtatttca ccagcaatta tgttgagaat aaggccaggc
4741 gaggtggctc acgcctgtaa tctcagcact ttgggaggcc agggcaggca gatcatctga
4801 ggtcaggagt ttgagaccag cctggccaac atggtgaaac cctatctcta ctaaaaatta
4861 aa

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D21254 Human mRNA for OB-Cadherin-1

1 cgcggagaga tgccgcgggg gccgctcgca gccgccgtg acttgtgaat gggaccggga
 61 ctggggccgg gactgacacc gcagcgcttg cctgcgcca gggactggcg gctcggaggt
 121 tgcgtccacc ctcaagggcc ccagaaatca ctgtgtttc agctcagcgg cctgtgaca
 181 ttccttcgtg ttgtcatttg ttgagtgacc aatcagatgg gtggagtgtg ttacagaaat
 241 tggcagcaag tatccaatgg gtgaagaaga agctaactgg ggacgtgggc agccctgacg
 301 tgatgagctc aaccagcaga gacattccat cccaagagag gtctgcgtga cgcgtccggg
 361 aggccaccct cagcaagacc accgtacagt tgggtgaagg ggtgacagct gcattctct
 421 gtgcctacca cgtaacaaa aatgaaggag aactactgtt tacaagccgc cctggtgtgc
 481 ctgggcatgc tgtgccacag ccatgccttt gcccagagc ggccggggca cctgcggccc
 541 tccttccatg ggcacatga gaagggaag gaggggcagg tgctacagcg ctccaagcgt
 601 ggctgggtct ggaaccagtt ctctgtgata gaggagtaca ccgggcctga cccgtgctt
 661 gtgggcaggc ttattcaga tattgactct ggtgatggga acattaaata cattcttca
 721 ggggaaggag ctggaacct tttgtgatt gatgacaaat cagggaacat tcatgccacc
 781 aagacgttgg atcgagaaga gagagcccag tacacgttga tggctcaggc ggtggacagg
 841 gacaccaatc ggccactgga gccaccgtcg gaattcattg tcaaggtcca ggacattaat
 901 gacaaccctc cggagttcct gcacgagacc tatcatgcca acgtgcctga gaggtccaat
 961 gtgggaacgt cagtaatcca ggtgacagct tcagatgcag atgacccac ttatggaat
 1021 agcgccaagt tagtgtacag tatcctcgaa ggacaacct attttcggg ggaagcacag
 1081 acaggtatca tcagaacagc cctaccaac atggacaggg aggccaaagga ggagtaccac
 1141 gtgtgatcc aggccaaagga catgggtgga catatgggcg gactctcagg gacaaccaa
 1201 gtgacgatca cactgaccga tgtcaatgac aaccaccaa agttccgca gagcgatac
 1261 cagatatctg tgcagaagc agccgtccct ggggaggaag taggaagagt gaaagctaaa
 1321 gatccagaca ttggagaaaa tggcttagtc acatacaata ttgtgatgg agatggtatg
 1381 gaatcgttgg aaatcacaaac ggactatgaa acacaggagg ggtgataaa gctgaaaaag
 1441 cctgtagatt ttgaaaccaa aagagcctat agcttgaagg tagaggcagc caacgtgcac
 1501 atcgaccgga agtttatcag caatggccct tcaaggaca ctgtgaccgt caagatcgca
 1561 gtagaagatg ctgatgagcc ccctatgttc ttggcccaa gttacatcca cgaagtcaa
 1621 gaaatgcag ctgctggcac cgtggttggg agagtgcag ccaaagacc tgatgctgcc
 1681 aacagccgga taagtattc catcgatcgt cactgacc tcgacagatt ttactatt
 1741 aatccagagg atgtttttat taaaactaca aaacctctgg atagagagga aacagcctgg
 1801 ctcaacatca ctgtctttgc agcagaaatc cacaatcggc atcaggaagc caaagtcca
 1861 gtggccatta ggttccttga tgtcaacgat aatgctcca agtttctgc ccctatgaa
 1921 ggtttcatct gtgagagtg tcaaccaag ccactttcca accagccaat tgtacaatt
 1981 agtgcatatg acaaggatga cagggccaat ggaccaagat ttattctcag cctacccct
 2041 gaaatcattc acaatccaaa ttccacagtc agagacaacc gagataaac agcaggcgtg
 2101 tacgcccggc gtggagggtt cagtcggcag aagcaggact tgtacctct gccatagtg
 2161 atcagcgatg gcggcatccc gccatgagt agcacaaca cctcaccat caaagtctgc
 2221 ggtgagcag tgaacggggc actgctctcc tgcaacgag aggcctacat tctgaacgc
 2281 ggctgagca caggcgccct gatcgccatc ctgcctgca tctcattct cctggtcatt
 2341 gtagtattgt ttgtgacct gagaaggcaa aagaagaac cactcattgt cttgaggaa
 2401 gaagatgtcc gtgagaacat cactactat gatgatgaag ggggtgggga agaagacaca
 2461 gaagcctttg atattgccac ctccagaat cctgatggt tcaatggatt tatccccgc
 2521 aaagacatca aacctgagta tcagtacatg cctagacctg ggctccggcc agcggccaa
 2581 agcgtggatg tcgatgact catcaacag agaatacagg aggcagacaa tgacccacg
 2641 gctctctct atgactccat tcaaatctac ggttatgaag gcaggggctc agtggccggg
 2701 tcctgagct ccctagagtc ggccaccaca gattcagact tggactatga ttatctacg
 2761 aactggggac ctgcttttaa gaaactagca gatttgtatg gtccaaaga cactttgat

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2821 gacgattctt aacaataacg atacaaattt ggccctaaga actgtgtctg gcgttctcaa
2881 gaatctagaa gatgtgtaaa caggtatttt tttaaataca ggaaaggctc atttaaaaca
2941 ggcaaagttt tacagagagg atacatttaa taaaactgcg aggacatcaa agtggtaaat
3001 actgtgaaat acctttctc acaaaaaggc aaatattgaa gttgtttatc aacttcgcta
3061 gaaaaaaaaa acactggca tacaaaatat ttaagtgaag gagaagtcta acgctgaact
3121 gacaatgaag ggaaattgtt tatgtgttat gaacatccaa gtctttctc tttttaagt
3181 tgtcaaagaa gcttcacaa aattagaaag gacaacagtt ctgagctgta atttcgcctt
3241 aaactctgga cactctatat gtagtgcatt tttaaactg aaatatataa tattcagcca
3301 gcttaaacc atacaatgta tgtacaatac aatgtacaat tatgtctctt gagcatcaat
3361 cttgttactg ctgattcttg taaatcttt tgcttctact tcatcttaa actaatcgt
3421 gccagatata actgtcttgt ttcagtgaga gacgccctat ttctatgtca ttttaagt
3481 atctatttgt acaattttaa agttcttatt ttagtatata tataaatatc agtattctga
3541 catgtaagaa aatgttacgg catcacactt atattttatg aacattgtac tgttgcttta
3601 atatgagctt caatataaga agcaatcttt gaaataaaaa aagatttttt tttaaaaaaa
3661 a

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D21255 Human mRNA for OB-cadherin-2

1 acaggcccg gacgtcccc tcagctggcg gcggccgcgg agagatgccg cgggggcccgc
 61 tcgcagcccg cgctgacttg tgaatgggac cgggactggg gccgggactg acaccgcagc
 121 gcttgccctg cgccagggac tggcggctcg gaggttgcgt ccaccctcaa gggccccaga
 181 aatcactgtg tticagctc agcggccctg tgacattcct tcgtgtgtc attgttgag
 241 tgaccaatca gatgggtgga gtgtgttaca gaaattggca gcaagtatcc aatgggtgaa
 301 gaagaagcta actggggacg tgggcagccc tgactgatg agtcaacca gcagagacat
 361 tccatcccaa gagaggtctg cgtgacgcgt ccgggaggcc accctcagca agaccaccgt
 421 acagttggtg gaaggggtga cagctgcatt ctctgtgcc taccacgtaa ccaaaaatga
 481 aggagaacta ctgtttacaa cccgccctgg tgtgcctggg catgctgtgc cacagccatg
 541 cctttgcccc agagcggcgg gggcacctgc ggccctcctt ccatgggcac catgagaagg
 601 gcaaggaggg gcaggtgcta cagcgtcca agcgtggctg ggtctggaac cagtcttcg
 661 tgatagagga gtacaccggg cctgacccc tgcttgggg caggcttcat tcagatattg
 721 actctgtgta tgggaacatt aaatacattc tctcagggga aggagctgga accattttg
 781 tgattgatga caaatcaggg aacattcatg ccaccaagac gttggatcga gaagagagag
 841 cccagtacac gttgatggct caggcgggtg acagggacac caatcgcca ctggagccac
 901 cgtcggaatt cattgtcaag gtccaggaca ttaatgacaa cctccggag ttcctgcacg
 961 agacctatca tgccaactg cctgagaggt ccaatgtggg aacgtcagta atccagggtga
 1021 cagcttcaga tgcatatgac ccacttatg gaaatagcgc caagttagtg tacagtatcc
 1081 tcgaaggaca accctatatt tcggtggaag cacagacagg tatcatcaga acagccctac
 1141 ccaacatgga caggagggcc aaggaggagt accacgtggt gatccaggcc aaggacatgg
 1201 gtggacatat gggcggactc tcagggacaa ccaaagtac gatcacactg accgatgtca
 1261 atgacaaccc accaaagttt ccgcagagcg tataccagat atctgtgtca gaagcagccg
 1321 tccctgggga ggaagtagga agagtgaag ctaaagatcc agacattgga gaaaatggct
 1381 tagtcacata caatattgtt gatggagatg gtatggaatc gtttgaaatc acaacggact
 1441 atgaacaca ggagggggtg ataaagctga aaaagcctgt agattttgaa accaaaagag
 1501 cctatagctt gaaggtagag gcagccaacg tgcacatcga ccgaagttt atcagcaatg
 1561 gccctttcaa ggacactgtg accgtcaaga tcgcagtaga agatgctgat gagcccccta
 1621 tgttcttggc ccaagttac atccacgaag tccaagaaaa tgcagctgct ggcaccgtgg
 1681 ttgggagagt gcatgccaaa gaccctgatg ctgccaacag ccgataagg tattccatcg
 1741 atcgtcacac tgacctgac agatttttca ctattaatcc agaggatggt ttattaaaa
 1801 ctacaaaacc tctgtagata gaggaacacg cctggctcaa catcactgtc ttgcagcag
 1861 aaatccacaa tcggcatcag gaagccaaag tccagtggc cattagggtc ctgatgtca
 1921 acgataatgc tccaagttt gctgccctt atgaaggtt catctgtgag agtgcacaga
 1981 ccaagccact ttcaaccag ccaattgtta caattagtgc agatgacaag gatgacacgg
 2041 ccaatggacc aagatttate ttcagcctac ccctgaaat cattcacaat ccaatttca
 2101 cagtcagaga caaccgagat aacacagcag gcgtgtacgc ccggcgtgga ggttcagtc
 2161 ggcagaagca ggactgtac ctctgccc tagtgatcag cgatggcggc atcccgcca
 2221 tgagtgcac caacacctc accatcaaag tctgcgggtg cgacgtgaac ggggcactgc
 2281 tctctgcaa cgcagaggcc tacattctga acgccggcct gagcacaggc gccctgatcg
 2341 ccatctcgc ctgcatctc attctctgg gttgccaag cttaatggaa cccccctc
 2401 ccagggaaga catgagattg ctctatctgg gctccagct gatgctatt tctatgtta
 2461 aagtaaacag aagattttgt ctctggggg tctttataaa acttcttct ctctatgtg
 2521 tggctacaga gactccaacc acacttacgt catttagta ttgttgtga cctgagaag
 2581 gcaaaagaaa gaaccttca ttgtcttga ggaagaagat gtccgtgaga acatcattac
 2641 ttatgatgat gaagggggtg gggaagaaga cacagaagcc ttgatattg ccaccctca
 2701 gaatctgat ggtatcaatg gatttatccc ccgcaaagac atcaaacctg agtatcagta
 2761 catgcctaga cctgggctcc ggccagcgc caacagcgtg gatgtcgtg acttcatcaa

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2821 cacgagaata caggaggcag acaatgaccc cacggctcct ccttatgact ccattcaaat
2881 ctacggttat gaaggcaggg gtcagtggc cgggtccctg agctccctag agtcggccac
2941 cacagattca gacttgact atgattatct acagaactgg ggacctcgtt ttaagaaact
3001 agcagatttg tatggttcca aagacacttt tgatgacgat tcttaacaat aacgatacaa
3061 atttggcctt aagaactgtg tctggcggtc tcaagaatct agaagatgtg taaacaggta
3121 ttttttaaa tcaaggaaag gtcatttaa aacaggcaaa gttttacaga gaggatacat
3181 ttaataaaac tgcgaggaca tcaaagtggt aaatactgtg aaataccttt tctcacaaaa
3241 aggcaaatat tgaagttgtt tatcaacttc gctagaaaaa aaaaacactt ggcatacaaa
3301 atatttaagt gaaggagaag tctaacgctg aactgacaat gaagggaaat tgtttatgtg
3361 ttatgaacat ccaagtcttt cttctttttt aagttgtcaa agaagcttcc acaaaattag
3421 aaaggacaac agttctgagc tgtaatttcg ccttaaacctc tggacactct atatgtagt
3481 catttttaaa cttgaaatat ataatttca gccagcttaa acccatacaa tgtatgtaca
3541 atacaatgta caattatgtc tcttgagcat caatcttgtt actgctgatt cttgtaaate
3601 tttttgcttc tactttcctc ttaactaat acgtgccaga tataactgtc ttgttcagt
3661 gagagacgcc ctatttctat gtcattttta atgtatctat ttgtacaatt ttaaagttct
3721 tatttttagta tacatataaa tatcagtatt ctgacatgta agaaaatgtt acggcatcac
3781 acttatattt tatgaacatt gtactgtgc tttaatga gcttcaatat aagaagcaat
3841 ctttgaata aaaaaagatt tttttt

Figure 24. (Page 36 of 46)**NM_014935 Homo sapiens phosphoinositol 3-phosphate-binding protein-3 (PEPP)**

1 gctggatcct gcagtaacca caacagcatc ctctccctgc gccagggacc tgccagccgg
 61 agagatgact gattagatca gattagatcc ggagccccgc tctgcagaag ggggccccag
 121 gggcggggga ggaggacccc agctggcctg agctgggggg aggggtgcct tggggctcgc
 181 agagttagag cttccagcg cggggatcac acctcagaag ccgccacaat gaaagacgga
 241 acacatttct acaccagtgc actggccagg tcccagagga aaacaaaaaa ttgacttga
 301 aaatatgcac ctggacatg tccaataaaa caggtgggaa acgcccggct accaccaaca
 361 gtgacatacc caaccacaac atggtgtccg aggtccctcc agagcggccc agcgtccggg
 421 caactcgcac agcccgcaa gccatgcct ttggcaagcg ctcacactcc atgaagcgga
 481 acccaatgc acctgtacc aaggcgggct ggctcttcaa acaggccagc tccggggta
 541 agcagtggaa caagcgctgg ttcgtcctgg tggatcgtc cctctctac tataaagatg
 601 agaaggaaga gattatcctg ggcagcatcc cctcctgag cttccgggta gccgcagtgc
 661 agccctcaga caacatcagc cggaacaca cgtttaaggc tgagcatgcc ggggtccgca
 721 cctactctt cagtcccgag agccccgagg agcaagaggc ctggatccag gccatggggg
 781 aggtgctcg agtacagatc cctccagccc agaagtcatg gccccaagct gtgcggcaca
 841 gccatgagaa gccagactcg gagaacgtcc caccagcaa gcaccaccag cagccacccc
 901 acaacagcct cctaagcct gagccagagg ccaagactcg aggggagggg gatggccgag
 961 gctgtgagaa ggagagaga aggcctgaga ggccagaagt caagaaagag cctccgggta
 1021 aagccaatgg cctccagct ggaccggagc cagcctcaga gccgggcagc ccttccccg
 1081 agggcccaag agtgccaggg ggtggggaac agcctgccca gcccaatggc tggcagtacc
 1141 actcccaag ccggccaggg agcacagctt tcccgtctca ggatggagag actgggggac
 1201 accggcgagg tttccacca cgcaccaacc ctgacaaaat tgcccagcgc aagagctcca
 1261 tgaaccagct tcagcagtgg gtgaatctgc gccggggggg accccgcct gaagacctc
 1321 ggagtccttc taggttctat cctgtgtctc gcagggtccc tgagtactat ggcccctact
 1381 cctccagta cccgatgat tatcagtact acccgccagg agtgcggccg gagagcatct
 1441 gttccatgcc ggccatgat cggatcagcc cggcctgggc cctggaggac aagcgccatg
 1501 cctccgcaa tgggggtggc cctgcctacc agctgcgaga gtggaaggag cccgccagct
 1561 acgggcggca ggatgccacc gtctggatcc caagcccctc ccggcagcca gtctattatg
 1621 atgagctgga tgcgcctct agtccctgc gccgcctgtc cctgcagccc cgtcccaact
 1681 ctgtgccccg ctacccagc cagggtcct acagcgtgc ccgcattac tcccctgtcc
 1741 gctaccccag tgcctgttt gagcggctgc cacctcgag tgaggacatc tatgttgacc
 1801 ctgtgccta tgtgatgagg cgtccatca gctccccc aaagtcccca taccagaag
 1861 tgttccggga cagcctccac acctacaagt taaacgagca agacacagat aagctgctgg
 1921 gaaaattgtg tgagcagaac aagggtgtga gggagcagga ccggctggtg cagcagctcc
 1981 gagctgagaa ggagagcctg gaaagtgcct tgatggggac ccaccaggag ctggagatgt
 2041 ttggaagcca gccgcctac ccagaaaagc tgcgacaaa aaaggattca ctgcagaacc
 2101 agctcatcaa catccgctg gagctgtctc aggcgaccac ggccctgaca aacagcacca
 2161 tagagtatga gcacctgag tctgaggtct ctgcctgca cgtgacctc tgggagcagc
 2221 tcaatttga caccagaat gaggtgctga accggcaaat ccaaaaggag atctggagga
 2281 tccaggacgt gatggagggg ctgaggaaga acaaccctc ccggggcacg gacaccgcca
 2341 agcacagagg aggaattggc cctcagcca cctacagctc caacagcccc gccagcccc
 2401 tcagctctgc cagcctacc agccccctga gcccctttc actggtgtcg ggctctcagg
 2461 ggtccccac caagcctggc tccaacgagc ccaaggcaaa ctatgaacaa agcaagaaag
 2521 acccccacca gacattgccc ctggacacc ccagagacat cagccttgtg cccaccaggc
 2581 aagaggtaga ggagagaag caggcagctc tcaacaaagt tggcgtgtg cccctcgga
 2641 caaatcgcc cactgatgat gaggtgacct catcagcagt ggtaagaagg aatgccagt
 2701 ggctaccaa tggactctcc tcccaggaac gcccgaagag tctgtgttt cctggcgagg
 2761 ggaaggtcaa gatgagcgtg gaggagcaga ttgaccgaat gcggcgccac cagagtggct

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2821 ccatgaagga gaagcggagg agcctgcagc tcccggccag cccggccccc gaccccagtc
2881 cccggccagc ctacaaagt gtgcgccgcc accgcagcat ccacgaggta gacatctcca
2941 acctggaggc agccctgcgg gcagaggagc ctggcgggca tgcctacgag acacccggg
3001 aggaaattgc cggcttcgc aaaatggagc tagagcccca gcattatgac gtggacatca
3061 ataaggagct ctccactcca gacaaagtcc tcacccctga acggtacatt gacctggagc
3121 ctgacactcc cctgagccct gaggagtga aggagaagca gaagaagggtg gagaggatca
3181 agacactcat tgccaaatcc agtatgcaga acgtggtgcc catcggcgag ggggactctg
3241 tggacgtgcc ccaggactca gagagccagc tgcaggagca ggagaagcgg attgaaatct
3301 cctgcgccct ggcgaccgag gcctcccgca ggggccgcat gctgtctgtg caatgtgcca
3361 cccaagccc tcccactcc cctgttccc cggtctctcc agcaaacccc ctgtcgtctg
3421 aatccccacg gggcgccgac agcagctata ccatgcgggt ctgagctctg actgcaagcc
3481 ctgggtgagg ccaatgtgt gaagctccac agagccacat tctgaagccg tcctctgccc
3541 acctgaggtc ctggtcccc accctggccc cctgcccctg cactcccatg ggaatgccgc
3601 agggagccag gctggggcca tgggctgtctg ccagaggacc gtggatacct cagtgtccac
3661 acaccacca tcccagccc tggagccatc actactaca ccgtggctct gggccagggc
3721 ctgagatgac agtggggagc accatcctca ttaatgtcca agtcacaggg agcctcagcc
3781 ttgcccctggc tggggtgtg gtgactccag tggaaacatc cctgatgggg gacatgccgt
3841 ggtggagaac acacctgttg ctatcttatg ttaggactag aggtgaagag gagatggaca
3901 ctgctctgg agccagcctg acaccaagga cagcacttgt catcatccct atcctcgtca
3961 gccccacct gctgcctcag ctggaccag ggcttgaca caaacccagt gctttgctta
4021 tgggtgctcg ctggggtccg gtggagactg accaccctgc ttgagccaaa gacaagggtga
4081 tgagagatgg ggagaggcca ttggtccca gaggaacag tgctggctgt ggctagagaa
4141 cagcaggtct gtgcagtgtc tgagggcagg ttgggaaggg tagcagagag agagagacag
4201 aaagagagag agagagagag agagagagag agagagagag agagagatcc tcagagtgga
4261 aggaggggga agcagcagga cacattggca agtcaagcag gaaggaggga gatggaaagg
4321 ggatatcaga ttggtttccc ccggtggagc cttaggttag tgcccagtc agtgccagac
4381 tgtctctct gtcctccca cctcatccct aggaggaccc accagtggag cacatgcagc
4441 ctacgtggag atgcttggtg tggggatctg ggtgaagggg gttagtagc gactgcctgg
4501 gagatggctg ttagtaggtc tgcgcctggt gtctgcctcg ccacctggg gtaaggggca
4561 gagagaagga ctgtcttat gtagggtgtg gtcagccttg gggccttacc taccagttc
4621 catgatattt ctgcccctgt tcccctgga atgtgcagtg ggccagctga gactacgcct
4681 ttaggagggg ggataggcc ttaatctggg aggcctatcc ccctatccca ggcatccag
4741 acgaggactg gctgaggcta ggcgtctca tgatccacct gcccgggag ggcagcggg
4801 aagacagaga aaagcaaaca cattcctct cagctccacc cacctggaga cgaatgtagc
4861 cagagaggag gaaggaggga aactgaaaac accgtggccc ctggccttc tctctgtag
4921 agttgccgt cagaggcttc agcctgactt ccagcggtec caagaacacc tactaatcc
4981 tctccactcc tcatggctg ggacagttac tggttcatat gcaagtaaag atgacaattt
5041 actcaac

Figure 24. (Page 38 of 46)**M61906 Human PI3-kinase, p85 subunit**

1 tacaaccagg ctcaactgtt gcatggtagc agatttgcaa acatgagtgc tgaggggtac
 61 cagtacagag cgctgtatga ttataaaaag gaaagagaag aagatattga ctgcacttg
 121 ggtgacatat tgactgtgaa taaaggggtcc ttagtagctc ttggattcag tgatggacag
 181 gaagccaggc ctgaagaaat tggctggta aatggctata atgaaaccac aggggaaagg
 241 ggggactttc cgggaactta cgtagaatat attggaagga aaaaaatctc gcctcccaca
 301 ccaaagcccc ggccacctcg gcctcttctt gttgcaccag gtcttcgaa aactgaagca
 361 gatgtgaac aacaagcttt gactctcccg gatcttgac agcagtttgc cctcctgac
 421 attgccccgc ctcttcttat caagctcgtg gaagccattg aaaagaaagg tctggaatgt
 481 tcaactctat acagaacaca gagctccagc aacctggcag aattacgaca gcttcttgat
 541 tgtgatacac cctccgtgga cttggaaatg atcgatgtgc acgttttggc tgacgcttc
 601 aaacgctatc tctggactt accaaatcct gtcattccag cagccgttta cagtgaatg
 661 atttcttag ctccagaagt acaaagctcc gaagaatata ttcagctatt gaagaagctt
 721 attaggtcgc ctacataacc tcatcagat tggcttacgc ttcagtattt gttaaacaat
 781 ttcttcaagc tctctcaaac ctccagcaaa aatctgttga atgcaagagt actctctgaa
 841 attttcagcc ctatgctttt cagattctca gcagccagct ctgataatac tgaaaacctc
 901 ataaaagtta tagaaatttt aatctcaact gaatggaatg aacgacagcc tgcaccagca
 961 ctgcctccta aaccacaaaa acctactact gtagccaaca acggtatgaa taacaatatg
 1021 tccttacaaa atgtcgaatg gtactgggga gatattctga ggggaagaat gaatgaaaaa
 1081 ctcgagata cagcagacgg gaccttttg gtacgagatg cgctactaa aatgcatggt
 1141 gattatactc ttacactaag gaaaggggga aatacaaat taatcaaat atttcatcga
 1201 gatgggaaat atggcttctc tgaccatta acctcagtt ctgtggttga attaataaac
 1261 cactaccgga atgaatctct agctcagat aatcccaat tggatgtgaa attactttat
 1321 ccagtatcca aataccaaca ggatcaagt gtcaaagaag ataatttga agctgtaggg
 1381 aaaaaattac atgaatataa cactcagtt caagaaaaaa gtcgagaata tgatagatta
 1441 tatgaagaat ataccgcac atcccaggaa atccaatga aaaggacagc tattgaagca
 1501 ttaattgaaa ccataaaaaa atttgaagaa cagtgccaga ccaagagcg gtacagcaaa
 1561 gaatacatag aaaagttaa acgtgaaggc aatgagaaag aaatacaaag gattatgat
 1621 aattatgata agttgaagtc tgaatcagt gaaattattg acagtagaag aagattggaa
 1681 gaagacttga agaagcaggc agctgagat cgagaaattg acaaacgtat gaacagcatt
 1741 aaaccagacc ttatccagct gagaaagac agagaccaat acttgatgtg gttgactcaa
 1801 aaaggtgttc ggcaaaagaa gttgaacgag tggttgggca atgaaaacac tgaagacca
 1861 tattactgg tggaagatga tgaagattg ccccatcatg atgagaagac atggaatgtt
 1921 ggaagcagca accgaaaca agctgaaaac ctgttgagc ggaagcgaga tggcactttt
 1981 ctgtccggg agagcagtaa acagggctgc tatgcctgct ctgtagtgtt ggacggcgaa
 2041 gtaaagcatt gtgtcataaa caaaacagca actggctatg gctttgccga gccctataac
 2101 ttgtacagct ctctgaaaga actggtgcta cattaccaac acacctccct tgtgcagcac
 2161 aacgactccc tcaatgtcac actagcctac ccagtatatg cacagcagag gcgatgaagc
 2221 gcttactctt tgatcttct cctgaagtc agccacctg aggcctctgg aaagcaaagg
 2281 gctcctctcc agtctgatct gtgaattgag ctgcagaaac gaagccatct tctttggat
 2341 gggactagag ctttcttca caaaaaagaa gtaggggaag acatgcagcc taaggctgta
 2401 tgatgaccac acgttctaa gctggagtgc ttatccctt ttttcttt tttcttgg
 2461 ttaatttaaa gccacaacca catacaacac aaagagaaaa agaaatgcaa aaatctctgc
 2521 gtgcagggac aaagaggcct ttaacctgg tgcctgttaa tgccttctga agctttacca
 2581 gctgaaagt gggactctgg agagcggagg agagagaggc agaagaacc tggcctgaga
 2641 aggtttgttc cagcctggt tagcctggat gttgctgtgc acggtggacc cagacacatc
 2701 gcactgtgga ttatttcatt ttgtaacaaa tgaacgatat gtagcagaaa ggcacgtcca
 2761 ctcaacagg acgctttggg agaattgcag ttcattgatg ttcagaagaa attctgtcat

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2821 agaaagtgcc agaaagtgtt taacttgtca aaaaacaaaa acccagcaac agaaaaatgg
2881 agtttgaaa acaggactta aaatgacatt cagtatataa aatatgtaca taatattgga
2941 tgactaacta tcaaatagat ggatttgtat caataccaaa tagcttctgt ttgttttgc
3001 tgaaggctaa attcacagcg ctatgcaatt ctaattttc attaagttgt tattcagtt
3061 ttaatgtac cttcagaata agcttcccca cccagtttt tgttgcttga aaatattgtt
3121 gtcccggtt ttgttaata ttcattttg ttatccttt ttaaaaataa atgtacagga
3181 tgccagtaaa aaaaaaatg gcttcagaat taaaactatg aaatattta cagttttct
3241 tgtacagagt acttgctgtt agccaaggt taaaagtgc ataacagatt tttttggac
3301 tgttttgtg ggcagtgcct gataagctc aaagctgctt tattcaataa aaaaaaac
3361 cgaattcact gg .

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J05582 Human mucin 1

1 ccgtccacc tctcaagcag ccagcgctg cctgaatctg ttctgcccc tccccacca
61 ttaccacc accatgacac cgggcacca gtctcttc ttctgctgc tgetctac
121 agtgcttaca gttgttacag gttctgtca tgcaagctt accccaggtg gagaaaagga
181 gacttcggt acccagagaa gttcagtcc cagctctact gagaagaatg ctgtgagtat
241 gaccagcagc gtacttcca gccacagccc cggttcagc tctccacca ctgaggaca
301 ggatgtcact ctggccccgg ccacggaacc agcttcaggt tcagtgcca ctggggaca
361 ggatgtcacc tcggccccag tcaccaggcc agccctgggc tccaccacc cggcagcca
421 cgatgtcacc tcagccccgg acaacaagcc agccccgggc tccaccgcc cccagcca
481 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
541 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
601 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
661 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
721 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
781 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
841 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
901 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
961 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1021 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1081 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1141 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1201 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1261 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1321 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1381 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1441 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1501 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1561 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
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1681 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1741 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1801 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1861 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1921 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
1981 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2041 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2101 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2161 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2221 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2281 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2341 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2401 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2461 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2521 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2581 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2641 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2701 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca
2761 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagcca

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2821 cgggtgcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2881 tgggtgcacc tcggccccgg acaacaggcc cgcttgggc tccaccgccc ctccagtcca
2941 caatgtcacc tcggcctcag gctctgcac aggtcagct tctactctgg tgcacaacgg
3001 cactctgcc agggctacca caaccccagc cagcaagagc actccattct caattcccag
3061 ccaccactct gatactcta ccaccttgc cagccatagc accaagactg atgccagtag
3121 cactcaccat agctcggtag ctctctcac ctctccaat cacagcactt ctccccagt
3181 gtctactggg gtctcttct tttctgtc tttcacatt tcaaacctcc agtttaattc
3241 ctctctggaa gatcccagca cggactacta ccaagagctg cagagagaca tttctgaaat
3301 gttttgcag atttataaac aaggggggtt tctgggcctc tccaatafta agttcaggcc
3361 aggatctgtg gtgttacaat tgactctggc ctccgagaa ggtaccatca atgtccacga
3421 cgtggagaca cagttcaatc agtataaaac ggaagcagcc tctcgatata acctgacgat
3481 ctcagacgtc agcgtgagtg atgtgccatt tctttctct gcccagtctg gggctgggggt
3541 gccaggctgg ggcacgcgc tgcgtgtgt ggtctgtgt ctggttgcgc tggccattgt
3601 ctatctcatt gccttggtg tctgtcagt cgcgcgaaag aactacgggc agctggacat
3661 ctttcagcc cgggatacct accatctat gacgagtag cccacctacc acacctatg
3721 gcgctatgtg cccctagca gtaccgatc tagccctat gagaagggtt ctgcaggtaa
3781 cgggtggcagc agcctctctt acacaaacc agcagtggca gccgttctg ccaactgta
3841 gggcacgtcg ccgtgagct gagtggccag ccagtccat tccactccac tcaggttctt
3901 caggccagag cccctgcacc ctgttgggc tggtagctg ggagttcagg tgggctgctc
3961 acagcctct tcagaggccc caccaatttc tcggacactt ctcagtgtgt ggaagctcat
4021 gtggggccct gaggtcatg cctgggaagt gttgtggggg ctcccaggag gactggccca
4081 gagagccctg agatagcggg gatcctgaac tggactgaat aaaacgtggt ctcccactg

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M29366 Human Epidermal Growth Factor Receptor (ErbB3)

1 accaatgcg cagcgggtca ggtggctctt gcctcgatgt cctagcctag gggccccgg
 61 gccggacttg gctgggctcc cttcaccctc tgcggagtca tgaggggcga cgacgctctg
 121 cagggtgctg gcttgctttt cagcctggcc cggggctccg aggtgggcaa ctctcaggca
 181 gtgtgtcctg ggactctgaa tggcctgagt gtgaccggcg atgctgagaa ccaataccag
 241 aactgtaca agctctacga gaggtgtgag gtggtgatgg ggaaccttga gattgtgctc
 301 acgggacaca atgccgacct ctcttcctg cagtggattc gagaagtgc aggctatgtc
 361 ctctgggcca tgaatgaatt ctctactcta ccattgccc acctccgct ggtgcgaggg
 421 acccaggtct acgatgggaa gtttgccatc ttgctcatgt tgaactataa caccaactcc
 481 agccacgctc tgcgccagct ccgcttgact cagtcaccg agattctgtc aggggggtgt
 541 tatattgaga agaacgataa gctttgtcac atggacacaa ttgactggag ggacatcgtg
 601 agggaccgag atgctgagat agtgggaag gacaatggca gaagctgtcc cccctgtcat
 661 gaggtttgca agggggcgtg ctggggctct ggatcagaag actgccagac attgaccaag
 721 accatctgtg ctctcagtg taatggtcac tgccttgggc ccaaccccaa ccagtgtgctc
 781 catgatgagt gtgccggggg ctgctcaggc cctcaggaca cagactgctt tgcctgccgg
 841 cacttcaatg acagtggagc ctgtgtacct cgtgtccac agcctctgt ctacaacaag
 901 ctaactttcc agctggaacc caatccccac accaagtatc agtatggagg agtttgtta
 961 gccagctgtc ccataactt tgtggtgat caaacatct gtgtcagggc ctgtctctct
 1021 gacaagatgg aagtagataa aaatgggctc aagatgtgtg agccttgtgg gggactatgt
 1081 cccaaagcct gtgagggaa aggctctggg agccgcttc agactgtgga ctcgagcaac
 1141 attgatggat ttgtgaactg caccaagatc ctgggcaacc tggactttct gatcacggc
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 1261 cggacagtac gggagatcac aggttacctg aacatccagt cctggccgcc ccacatgcac
 1321 aacttcagt tttttccaa ttgacaacc attggaggca gaagcctcta caaccggggc
 1381 ttctcattgt tgatcatgaa gaactgaat gtcacatctc tgggcttcg atccctgaag
 1441 gaaattagt ctgggcgtat ctatataagt gccaataggc agctctgcta ccaccactct
 1501 ttgaactgga ccaaggtgct tggggggcct acggaagagc gactagacat caagcataat
 1561 cggccgcgca gagactgctg ggcagagggc aaagtgtgtg acccactgtg ctctctggg
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 1981 gactgttag gacaaact ggtgctgac ggcaaaacc atctgacaat ggcttgaca
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 2521 ccacagctgc tgcctaactg gggagtacaa attgccaagg gaatgtacta ccttgaggaa
 2581 catggtatgg tgcatagaaa cctggctgcc cgaacgtgc tactcaagtc acccagtcag
 2641 gttcaggtgg cagatttgg tgtggctgac ctgtgcctc ctgatgataa gcagctgcta
 2701 tacagtgagg ccaagactcc aattaagtgg atggcccttg agagtatcca ctttgggaaa
 2761 tacacacacc agagtgtatg ctggagctat ggtgtgacag ttgggagtt gatgacctc

Figure 24. (Page 43 of 46)

2821 ggggcagagc cctatgcagg gctacgattg gctgaagtac cagacctgct agagaagggg
2881 gagcgggttg cacagcccca gatctgcaca attgatgtct acatgggtgat ggtcaagtgt
2941 tggatgattg atgagaacat tcgccaacc tttaaagaac tagccaatga gttcaccagg
3001 atggcccag acccaccag gtatctggtc ataaagagag agagtgggccc tggaatagcc
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4621 tattgattac tatcataatt cagcacttaa ctatgagcca ggcatacat taaactcac
4681 ctacattatc tcaacttagt ctttatcatc cttaaaacaa ttctgtgaca tacatattat
4741 ctcatcttac acaaaggga gtcgggcatg gtggctcatg cctgtaact cagcatttg
4801 ggaggctgag gcagaaggat tacctgagc aaggagtgtg agaccagctt agccaacata
4861 gtaagacccc catctctt

Figure 24. (Page 44 of 46)**Homo sapiens gene for hepatitis C-associated microtubular aggregate protein p44****D28908 Exon 1 and 2**

1 gaattctgaa tataggacac gaatttatga tccttagcaa tgtgaagta gagaaggggt
61 ttattgtga aattgacaca ggttggttta tatcttataa atgaagtctc ctcattttcc
121 tgtggtcaga agagaggggg caagcagaaa agcagaggaa caaatttggg ggctaaaata
181 acattctaca taaggaacta tactacagta gaattaattg atagcaggga ttaagagatg
241 taaatgaatt tgagatacat attctagagg tagaatgtgc aatactttt gtatgtccat
301 atacagaaat tgggtgcatt ttccttaa ataaaagatt tttaaaagtc agtgagctgt
361 tatgtttct tcctctgac tcaattcct tgattcttc aatttttta atataaatt
421 actgtctaaa agctggatca gcttatgctc cttgttgag agaagttggc atgctgtcaa
481 gtgggctggg cactactgag ttactgttc ttctctgag tcttgaagc tcaaggctg
541 ctgaataatt tccttctccc atttgtgcc tgcctagcta tccagacaga gcagctacc
601 tcagctctag ctgatactac agacagtaca acaggtaa atgtttctgc tttcatttt
661 tcctagctag cattagtctc tctctgtctc tctcagggtga cagtgtccat tgcaatctca
721 gttttgttt taattaaaa aacaataatt tatagtaaaa aattagctaa tgatttttt
781 gcttctgtt cactcttgt ttgtcatt ttgtattat gtagagtata taagaggcat
841 aaatgcaaat ttataacta catattatct gttttta atttaatgga aaatatatat
901 gatttgccac tagatcaaga agtatggcag tgacaactcg ttgacatgg ttgcacgaaa
961 agatcctgca aaatcatttt ggagggaagc ggcttagcct tctctataag ggtagtgtcc
1021 atggattccg taatggagtt ttgcttgaca gatgtgttaa tcaagggcct actctaacag
1081 tgatttatag tgaagatcat attattggag catatgcaga agagagtac caggaaggaa
1141 agtatgctc catcatcctt ttgcactc aagatactaa aatttcagaa tggaaactag
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1261 attccagat agatggaaga aatagaaaag tgattatgga cttaaagaca atggaaaatc
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1441 caattcatct cttaaggaa aaatgaactt ttcactgtc aataatttgg atgattcaga
1501 ctgaaacctg gatacagatt gttgctaag agacaacat ggtcaataaa atgtatatt
1561 atgataagaa ccctaacgt aagatttatc ctcttagcac atttaagta c

D28909 Exon 3

1 gaattcactg atattcattc attcattcag ccaattatc gacaacttct aatctacatt
61 attctttgat tatttcccc gattcactgg atgaaagaaa gataaaaggg gtcattgagt
121 aagtcattgt ttttaagatt ctattactct ctcca

Figure 24. (Page 45 of 46)**D28910 Exon 4**

1 ttgcgacct aacctcagtc aattgttaaa aacggtcattg tctaaacagg ctcaggaaga
61 gcttactgtc tgccttgaga acttatgaac catatggatc cctgggtcaa caaatacgaa
121 ttctctctct gggccaatt ggagctccca agtccagctt ttcaactca gtgaggtctg
181 tttccaagg gcatgtaac catcaggctt tgggtgggcac taatacaact gggatatctg
241 agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaact caattatatt
301 tcaaaagctt tt

D28911 Exon 5

1 ggccacctag cctttgcttc tctgttcaaa tcaattatat ttcaaaagcc tttgcagat
61 caactttatt acatatagac ttcatctcaa ttataataa aaaatgaatc tttaaattg
121 cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac
181 ctgccgttta ttctgtgtga ctactgggg ctgagtgaga aagaaggcgg cctgtgcagg
241 gatgacatat tctatatctt gaacggtaac attcgtgata gataccagggt aatatttgac
301 taatgagaaa ttataactga tttttaaact gcttatttt gtacaaatgt atcagcgttt
361 atcttcttaa attatacttg ctcaagatcc ttgtctctt ttgattttt ttttcaaaa
421 agaataaaaa catctcgagg gctcttc

D28912 Exon 6

1 ttgtgctcat aaatatttgt tgaattaata tcttgcttta tgtctacctt acagttaat
61 cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac
121 agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctctctcag
181 atgatatgaa agatcaaaaag aattcaaagg gagttggtaa acgctgggtga gtctattcc
241 actttgctaa gggaataacc actaagggtta attgactaga ctgtatttta gaatgccttt
301 tggacaggat aaagaactta agtcattgca tattcaatc t

D28913 Exon 7

1 gatctttcca aatctgaaat tgttccatag gttgcctatt acataattga tagttaata
61 acttgaaaat actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg
121 tacatgtggc ttgtctact catgtggata gcatggattt gattacaaaa ggtgacctta
181 tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc ctctgtaaac
241 acattttctg gggatgttta ctacaatcac atactagtgt gtataaaa

Figure 24. (Page 46 of 46)**D28914 Exon 8**

1 ttttttcca atggaaatta ttgcaagttc ctacatcttg atattgcttt cataatttat
61 actaacataa aataatattt ttactgttt tgcaatgtct tttaatttc tgtattgcag
121 ctagaggaag tccaaagaaa acttggattt gctctttctg acatctcggg ggtagcaat
181 tattctctcg agtgggagct ggaccctgta aaggatgttc taattcttc tgctctgaga
241 cgaatgctat gggctgcaga tgactctta gaggatttgc cttttgagca aataggtaga
301 tggtttggg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttggatc
361 tattaaatac tg

D28915 Exon 9

1 cctctggttg cctttcctga gataatccac taagaatatt ttgtgtttct ttctcaggg
61 aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaagggtc
121 acgtaaattt cctcacatca cagaagatta aaattcagaa aggagaaaac acagaccaa
181 gagaagtatc taagaccaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata
241 gaacattgta gtacttgtaa ataactagaa ataacatgat ttagtcataa ttgtgaaaaa
301 taataataat tttcttggga ttatgttct gtatctgtga aaaaataaat ttcttataaa
361 actcgggtct aacttgagag tgtgtgtgat ttggaaaaa ttatgatttg tcagcatctt
421 ctgatattca ctgcttcat cttattttg ccttctgatt ttattctaa agtatgtgat
481 ttt

Figure 25.

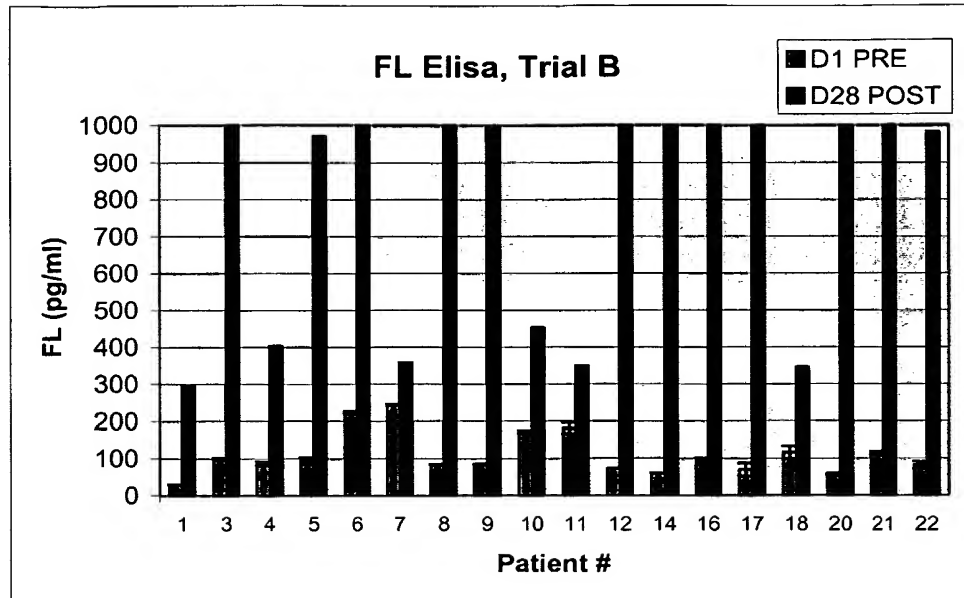


Figure 26.

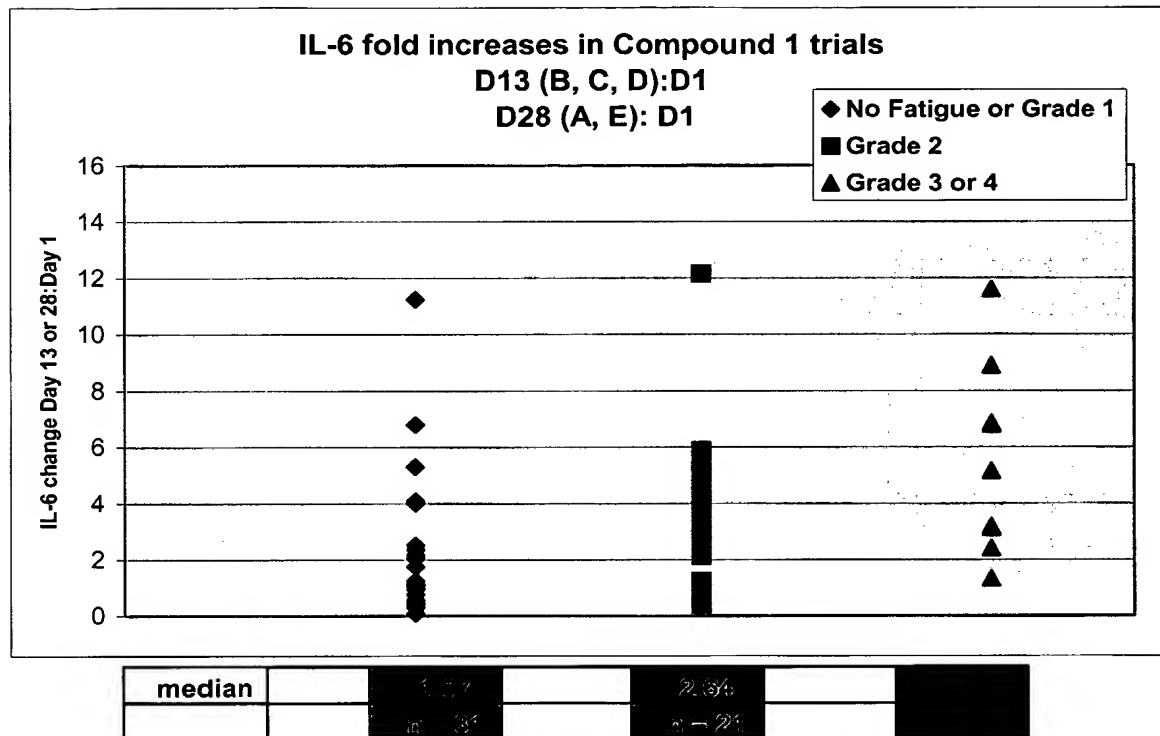


Figure 27.

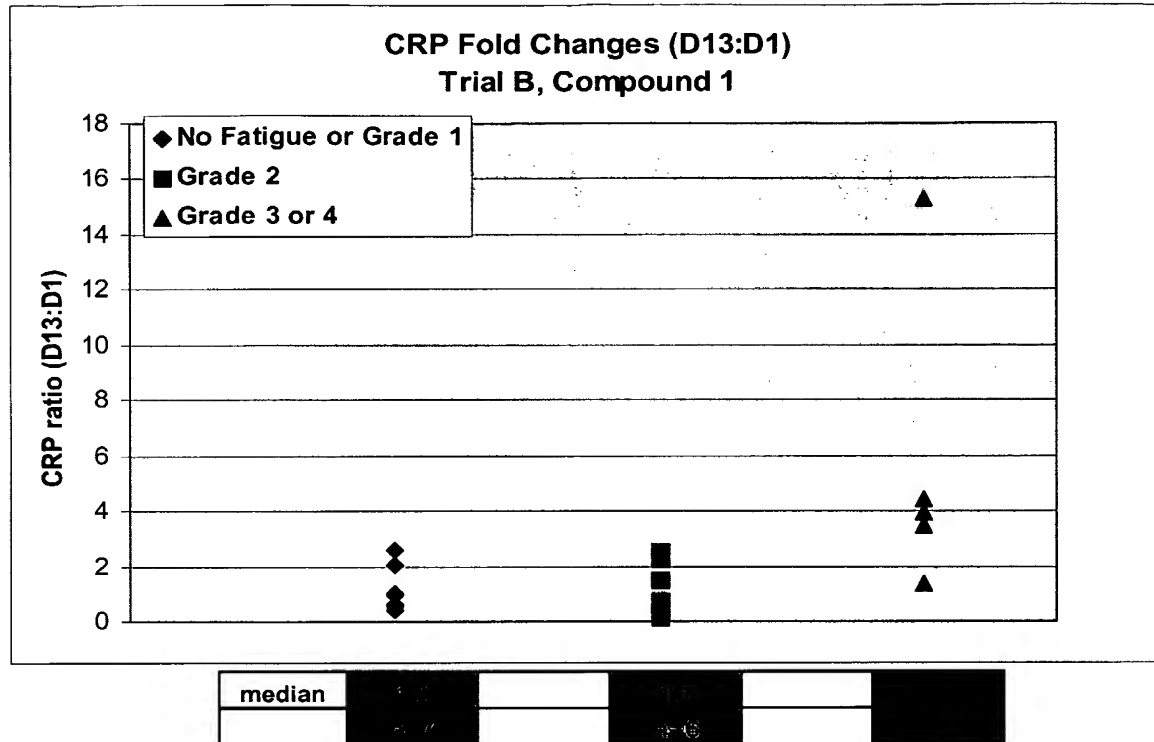
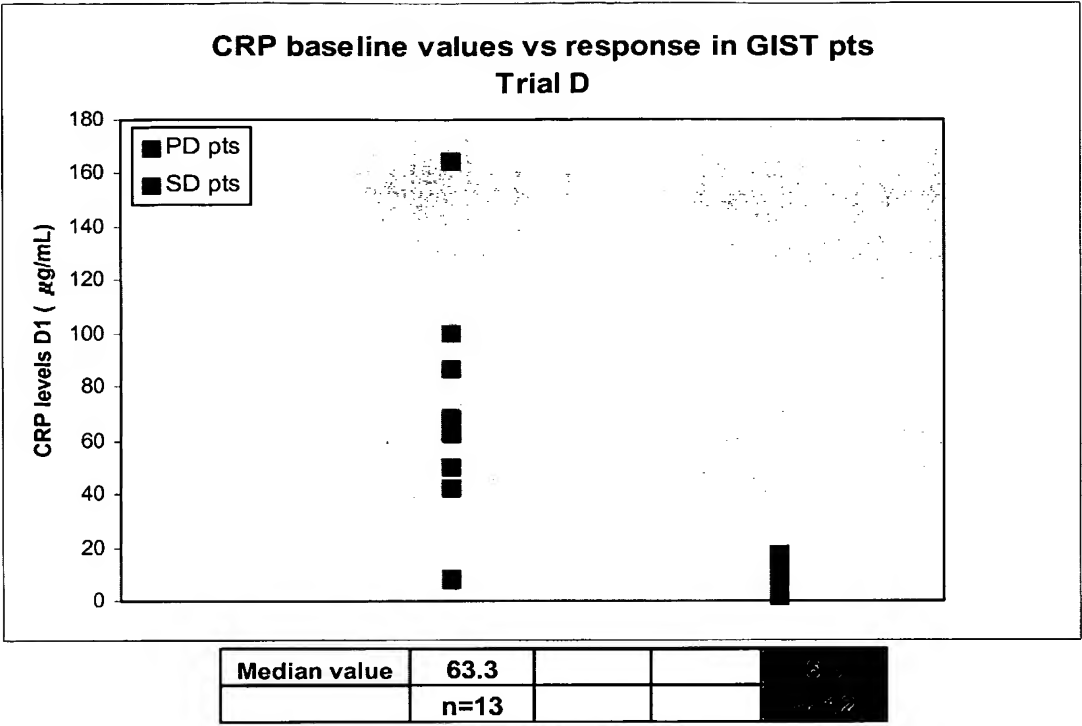


Figure 28.



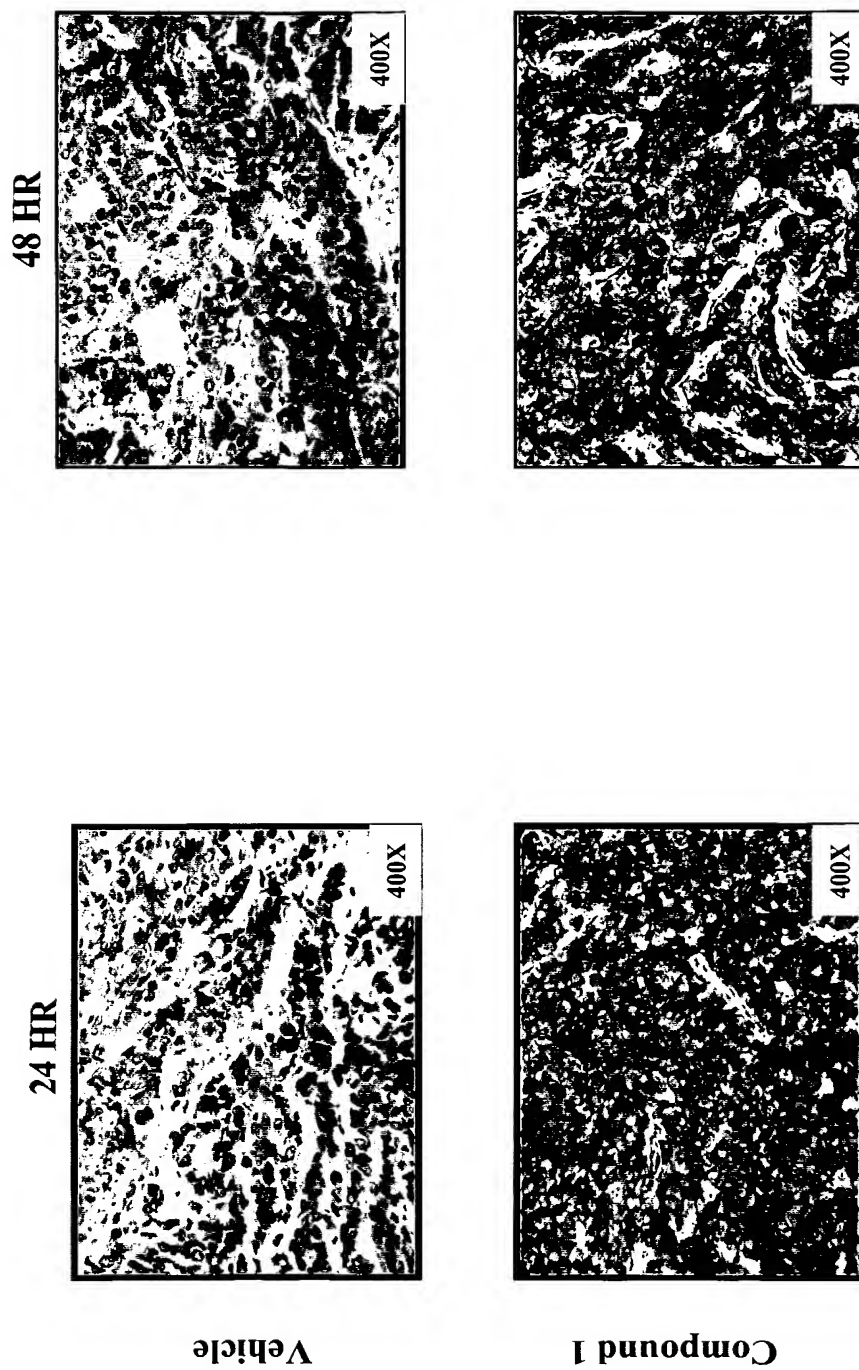


Figure 29.

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SEQUENCE LISTING

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<150> 60/448,922

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<151> 2003-02-24

<160> 185

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<210> 2

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<223> Description of Artificial Sequence: Primer

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<210> 3

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

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<212> DNA
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<220>

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<210> 13

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21

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<210> 35

<211> 20

<212> DNA

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<223> Description of Artificial Sequence: Primer

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<210> 36

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9/147

<212> DNA

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<210> 38

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<223> Description of Artificial Sequence: Primer

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<210> 39

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Probe

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<210> 40

<211> 26

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<223> Description of Artificial Sequence: Primer

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tctaccgtcc ttgtcataac tttgtg

26

<210> 41

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 41

atgatgatgg gccctgtt

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<210> 42
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 42
cctttgccca agttg 15

<210> 43
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 43
tggacgtttt gtgatcgaag ag 22

<210> 44
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 44
aagtcaaggc ttctgtcttt tcttct 26

<210> 45
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 45
cttgagaatc ctttccaacc 20

<210> 46
<211> 10
<212> PRT
<213> Homo sapiens

<400> 46
Asp Ile Tyr Ser Ser Phe Gly Phe Pro Arg
1 5 10

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<210> 47
 <211> 11
 <212> PRT
 <213> Homo sapiens

<400> 47
 Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg
 1 5 10

<210> 48
 <211> 114
 <212> PRT
 <213> Homo sapiens

<400> 48
 Met Ser Leu Leu Ser Ser Arg Ala Ala Arg Val Pro Gly Pro Ser Ser
 1 5 10 15
 Ser Leu Cys Ala Leu Leu Val Leu Leu Leu Leu Thr Gln Pro Gly
 20 25 30
 Pro Ile Ala Ser Ala Gly Pro Ala Ala Ala Val Leu Arg Glu Leu Arg
 35 40 45
 Cys Val Cys Leu Gln Thr Thr Gln Gly Val His Pro Lys Met Ile Ser
 50 55 60
 Asn Leu Gln Val Phe Ala Ile Gly Pro Gln Cys Ser Lys Val Glu Val
 65 70 75 80
 Val Ala Ser Leu Lys Asn Gly Lys Glu Ile Cys Leu Asp Pro Glu Ala
 85 90 95
 Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Gly Gly Asn Lys
 100 105 110
 Glu Asn

<210> 49
 <211> 120
 <212> PRT
 <213> Homo sapiens

<400> 49
 Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
 1 5 10 15
 Leu Gly Ser Gln Ala Arg Val Thr Lys Asp Ala Glu Thr Glu Phe Met
 20 25 30
 Met Ser Lys Leu Pro Leu Glu Asn Pro Val Leu Leu Asp Arg Phe His
 35 40 45
 Ala Thr Ser Ala Asp Cys Cys Ile Ser Tyr Thr Pro Arg Ser Ile Pro
 50 55 60

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Cys Ser Leu Leu Glu Ser Tyr Phe Glu Thr Asn Ser Glu Cys Ser Lys
 65 70 75 80
 Pro Gly Val Ile Phe Leu Thr Lys Lys Gly Arg Arg Phe Cys Ala Asn
 85 90 95
 Pro Ser Asp Lys Gln Val Gln Val Cys Met Arg Met Leu Lys Leu Asp
 100 105 110
 Thr Arg Ile Lys Thr Arg Lys Asn
 115 120

<210> 50
 <211> 902
 <212> PRT
 <213> Homo sapiens

<400> 50
 Met Ser Glu Phe Arg Ile His His Asp Val Asn Glu Leu Leu Ser Leu
 1 5 10 15
 Leu Arg Val His Gly Gly Asp Gly Ala Glu Val Tyr Ile Asp Leu Leu
 20 25 30
 Gln Lys Asn Arg Thr Pro Tyr Val Thr Thr Thr Val Ser Ala His Ser
 35 40 45
 Ala Lys Val Lys Ile Ala Glu Phe Ser Arg Thr Pro Glu Asp Phe Leu
 50 55 60
 Lys Lys Tyr Asp Glu Leu Lys Ser Lys Asn Thr Arg Asn Leu Asp Pro
 65 70 75 80
 Leu Val Tyr Leu Leu Ser Lys Leu Thr Glu Asp Lys Glu Thr Leu Gln
 85 90 95
 Tyr Leu Gln Gln Asn Ala Lys Glu Arg Ala Glu Leu Ala Ala Ala Ala
 100 105 110
 Val Gly Ser Ser Thr Thr Ser Ile Asn Val Pro Ala Ala Ala Ser Lys
 115 120 125
 Ile Ser Met Gln Glu Leu Glu Glu Leu Arg Lys Gln Leu Gly Ser Val
 130 135 140
 Ala Thr Gly Ser Thr Leu Gln Gln Ser Leu Glu Leu Lys Arg Lys Met
 145 150 155 160
 Leu Arg Asp Lys Gln Asn Lys Lys Asn Ser Gly Gln His Leu Pro Ile
 165 170 175
 Phe Pro Ala Trp Val Tyr Glu Arg Pro Ala Leu Ile Gly Asp Phe Leu
 180 185 190
 Ile Gly Ala Gly Ile Ser Thr Asp Thr Ala Leu Pro Ile Gly Thr Leu
 195 200 205

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Pro	Leu	Ala	Ser	Gln	Glu	Ser	Ala	Val	Val	Glu	Asp	Leu	Leu	Tyr	Val	210	215	220
Leu	Val	Gly	Val	Asp	Gly	Arg	Tyr	Val	Ser	Ala	Gln	Pro	Leu	Ala	Gly	225	230	235
Arg	Gln	Ser	Arg	Thr	Phe	Leu	Val	Asp	Pro	Asn	Leu	Asp	Leu	Ser	Ile	245	250	255
Arg	Glu	Leu	Val	His	Arg	Ile	Leu	Pro	Val	Ala	Ala	Ser	Tyr	Ser	Ala	260	265	270
Val	Thr	Arg	Phe	Ile	Glu	Glu	Lys	Ser	Ser	Phe	Glu	Tyr	Gly	Gln	Val	275	280	285
Asn	His	Ala	Leu	Ala	Ala	Ala	Met	Arg	Thr	Leu	Val	Lys	Glu	His	Leu	290	295	300
Ile	Leu	Val	Ser	Gln	Leu	Glu	Gln	Leu	His	Arg	Gln	Gly	Leu	Leu	Ser	305	310	315
Leu	Gln	Lys	Leu	Trp	Phe	Tyr	Ile	Gln	Pro	Ala	Met	Arg	Thr	Met	Asp	325	330	335
Ile	Leu	Ala	Ser	Leu	Ala	Thr	Ser	Val	Asp	Lys	Gly	Glu	Cys	Leu	Gly	340	345	350
Gly	Ser	Thr	Leu	Ser	Leu	Leu	His	Asp	Arg	Ser	Phe	Ser	Tyr	Thr	Gly	355	360	365
Asp	Ser	Gln	Ala	Gln	Glu	Leu	Cys	Leu	Tyr	Leu	Thr	Lys	Ala	Ala	Ser	370	375	380
Ala	Pro	Tyr	Phe	Glu	Val	Leu	Glu	Lys	Trp	Ile	Tyr	Arg	Gly	Ile	Ile	385	390	395
His	Asp	Pro	Tyr	Ser	Glu	Phe	Met	Val	Glu	Glu	His	Glu	Leu	Arg	Lys	405	410	415
Glu	Arg	Ile	Gln	Glu	Asp	Tyr	Asn	Asp	Lys	Tyr	Trp	Asp	Gln	Arg	Tyr	420	425	430
Thr	Ile	Val	Gln	Gln	Gln	Ile	Pro	Ser	Phe	Leu	Gln	Lys	Met	Ala	Asp	435	440	445
Lys	Ile	Leu	Ser	Thr	Gly	Lys	Tyr	Leu	Asn	Val	Val	Arg	Glu	Cys	Gly	450	455	460
His	Asp	Val	Thr	Cys	Pro	Val	Ala	Lys	Glu	Ile	Ile	Tyr	Thr	Leu	Lys	465	470	475
Glu	Arg	Ala	Tyr	Val	Glu	Gln	Ile	Glu	Lys	Ala	Phe	Asn	Tyr	Ala	Ser	485	490	495
Lys	Val	Leu	Leu	Asp	Phe	Leu	Met	Glu	Glu	Lys	Glu	Leu	Val	Ala	His	500	505	510

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Leu Arg Ser Ile Lys Arg Tyr Phe Leu Met Asp Gln Gly Asp Phe Phe
 515 520 525
 Val His Phe Met Asp Leu Ala Glu Glu Glu Leu Arg Lys Pro Val Glu
 530 535 540
 Asp Ile Thr Pro Pro Arg Leu Glu Ala Leu Leu Glu Leu Ala Leu Arg
 545 550 555 560
 Met Ser Thr Ala Asn Thr Asp Pro Phe Lys Asp Asp Leu Lys Ile Asp
 565 570 575
 Leu Met Pro His Asp Leu Ile Thr Gln Leu Leu Arg Val Leu Ala Ile
 580 585 590
 Glu Thr Lys Gln Glu Lys Ala Met Ala His Ala Asp Pro Thr Glu Leu
 595 600 605
 Ala Leu Ser Gly Leu Glu Ala Phe Ser Phe Asp Tyr Ile Val Lys Trp
 610 615 620
 Pro Leu Ser Leu Ile Ile Asn Arg Lys Ala Leu Thr Arg Tyr Gln Met
 625 630 635 640
 Leu Phe Arg His Met Phe Tyr Cys Lys His Val Glu Arg Gln Leu Cys
 645 650 655
 Ser Val Trp Ile Ser Asn Lys Thr Ala Lys Gln His Ser Leu His Ser
 660 665 670
 Ala Gln Trp Phe Ala Gly Ala Phe Thr Leu Arg Gln Arg Met Leu Asn
 675 680 685
 Phe Val Gln Asn Ile Gln Tyr Tyr Met Met Phe Glu Val Met Glu Pro
 690 695 700
 Thr Trp His Ile Leu Glu Lys Asn Leu Lys Ser Ala Ser Asn Ile Asp
 705 710 715 720
 Asp Val Leu Gly His His Thr Gly Phe Leu Asp Thr Cys Leu Lys Asp
 725 730 735
 Cys Met Leu Thr Asn Pro Glu Leu Leu Lys Val Phe Ser Lys Leu Met
 740 745 750
 Ser Val Cys Val Met Phe Thr Asn Cys Met Gln Lys Phe Thr Gln Ser
 755 760 765
 Met Lys Leu Asp Gly Glu Leu Gly Gly Gln Thr Leu Glu His Ser Thr
 770 775 780
 Val Leu Gly Leu Pro Ala Gly Ala Glu Glu Arg Ala Arg Lys Glu Leu
 785 790 795 800
 Ala Arg Lys His Leu Ala Glu His Ala Asp Thr Val Gln Leu Val Ser
 805 810 815

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Gly Phe Glu Ala Thr Ile Asn Lys Phe Asp Lys Asn Phe Ser Ala His
 820 825 830
 Leu Leu Asp Leu Leu Ala Arg Leu Ser Ile Tyr Ser Thr Ser Asp Cys
 835 840 845
 Glu His Gly Met Ala Ser Val Ile Ser Arg Leu Asp Phe Asn Gly Phe
 850 855 860
 Tyr Thr Glu Arg Leu Glu Arg Leu Ser Ala Glu Arg Ser Gln Lys Ala
 865 870 875 880
 Thr Pro Gln Val Pro Val Leu Arg Gly Pro Pro Ala Pro Ala Pro Arg
 885 890 895
 Val Ala Val Thr Ala Gln
 900

<210> 51
 <211> 252
 <212> PRT
 <213> Homo sapiens

<400> 51
 Met Arg Ala Pro Leu Leu Pro Pro Ala Pro Val Val Leu Ser Leu Leu
 1 5 10 15
 Ile Leu Gly Ser Gly His Tyr Ala Ala Gly Leu Asp Leu Asn Asp Thr
 20 25 30
 Tyr Ser Gly Lys Arg Glu Pro Phe Ser Gly Asp His Ser Ala Asp Gly
 35 40 45
 Phe Glu Val Thr Ser Arg Ser Glu Met Ser Ser Gly Ser Glu Ile Ser
 50 55 60
 Pro Val Ser Glu Met Pro Ser Ser Ser Glu Pro Ser Ser Gly Ala Asp
 65 70 75 80
 Tyr Asp Tyr Ser Glu Glu Tyr Asp Asn Glu Pro Gln Ile Pro Gly Tyr
 85 90 95
 Ile Val Asp Asp Ser Val Arg Val Glu Gln Val Val Lys Pro Pro Gln
 100 105 110
 Asn Lys Thr Glu Ser Glu Asn Thr Ser Asp Lys Pro Lys Arg Lys Lys
 115 120 125
 Lys Gly Gly Lys Asn Gly Lys Asn Arg Arg Asn Arg Lys Lys Lys Asn
 130 135 140
 Pro Cys Asn Ala Glu Phe Gln Asn Phe Cys Ile His Gly Glu Cys Lys
 145 150 155 160
 Tyr Ile Glu His Leu Glu Ala Val Thr Cys Lys Cys Gln Gln Glu Tyr
 165 170 175

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Phe Gly Glu Arg Cys Gly Glu Lys Ser Met Lys Thr His Ser Met Ile
 180 185 190

Asp Ser Ser Leu Ser Lys Ile Ala Leu Ala Ala Ile Ala Ala Phe Met
 195 200 205

Ser Ala Val Ile Leu Thr Ala Val Ala Val Ile Thr Val Gln Leu Arg
 210 215 220

Arg Gln Tyr Val Arg Lys Tyr Glu Gly Glu Ala Glu Glu Arg Lys Lys
 225 230 235 240

Leu Arg Gln Glu Asn Gly Asn Val His Ala Ile Ala
 245 250

<210> 52
 <211> 271
 <212> PRT
 <213> Homo sapiens

<400> 52
 Met Ala Lys Val Pro Asp Met Phe Glu Asp Leu Lys Asn Cys Tyr Ser
 1 5 10 15

Glu Asn Glu Glu Asp Ser Ser Ser Ile Asp His Leu Ser Leu Asn Gln
 20 25 30

Lys Ser Phe Tyr His Val Ser Tyr Gly Pro Leu His Glu Gly Cys Met
 35 40 45

Asp Gln Ser Val Ser Leu Ser Ile Ser Glu Thr Ser Lys Thr Ser Lys
 50 55 60

Leu Thr Phe Lys Glu Ser Met Val Val Val Ala Thr Asn Gly Lys Val
 65 70 75 80

Leu Lys Lys Arg Arg Leu Ser Leu Ser Gln Ser Ile Thr Asp Asp Asp
 85 90 95

Leu Glu Ala Ile Ala Asn Asp Ser Glu Glu Glu Ile Ile Lys Pro Arg
 100 105 110

Ser Ala Pro Phe Ser Phe Leu Ser Asn Val Lys Tyr Asn Phe Met Arg
 115 120 125

Ile Ile Lys Tyr Glu Phe Ile Leu Asn Asp Ala Leu Asn Gln Ser Ile
 130 135 140

Ile Arg Ala Asn Asp Gln Tyr Leu Thr Ala Ala Ala Leu His Asn Leu
 145 150 155 160

Asp Glu Ala Val Lys Phe Asp Met Gly Ala Tyr Lys Ser Ser Lys Asp
 165 170 175

Asp Ala Lys Ile Thr Val Ile Leu Arg Ile Ser Lys Thr Gln Leu Tyr
 180 185 190

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Val Thr Ala Gln Asp Glu Asp Gln Pro Val Leu Leu Lys Glu Met Pro
 195 200 205

Glu Ile Pro Lys Thr Ile Thr Gly Ser Glu Thr Asn Leu Leu Phe Phe
 210 215 220

Trp Glu Thr His Gly Thr Lys Asn Tyr Phe Thr Ser Val Ala His Pro
 225 230 235 240

Asn Leu Phe Ile Ala Thr Lys Gln Asp Tyr Trp Val Cys Leu Ala Gly
 245 250 255

Gly Pro Pro Ser Ile Thr Asp Phe Gln Ile Leu Glu Asn Gln Ala
 260 265 270

<210> 53
 <211> 269
 <212> PRT
 <213> Homo sapiens

<400> 53
 Met Ala Glu Val Pro Glu Leu Ala Ser Glu Met Met Ala Tyr Tyr Ser
 1 5 10 15

Gly Asn Glu Asp Asp Leu Phe Phe Glu Ala Asp Gly Pro Lys Gln Met
 20 25 30

Lys Cys Ser Phe Gln Asp Leu Asp Leu Cys Pro Leu Asp Gly Gly Ile
 35 40 45

Gln Leu Arg Ile Ser Asp His His Tyr Ser Lys Gly Phe Arg Gln Ala
 50 55 60

Ala Ser Val Val Val Ala Met Asp Lys Leu Arg Lys Met Leu Val Pro
 65 70 75 80

Cys Pro Gln Thr Phe Gln Glu Asn Asp Leu Ser Thr Phe Phe Pro Phe
 85 90 95

Ile Phe Glu Glu Glu Pro Ile Phe Phe Asp Thr Trp Asp Asn Glu Ala
 100 105 110

Tyr Val His Asp Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp
 115 120 125

Ser Gln Gln Lys Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala
 130 135 140

Leu His Leu Gln Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met
 145 150 155 160

Ser Phe Val Gln Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu
 165 170 175

Gly Leu Lys Glu Lys Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp
 180 185 190

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Lys Pro Thr Leu Gln Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys
 195 200 205
 Lys Lys Met Glu Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn
 210 215 220
 Lys Leu Glu Phe Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr
 225 230 235 240
 Ser Gln Ala Glu Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly
 245 250 255
 Gln Asp Ile Thr Asp Phe Thr Met Gln Phe Val Ser Ser
 260 265

<210> 54
 <211> 153
 <212> PRT
 <213> Homo sapiens

<400> 54
 Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
 1 5 10 15
 Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
 20 25 30
 Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
 35 40 45
 Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
 50 55 60
 Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
 65 70 75 80
 Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
 85 90 95
 Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
 100 105 110
 Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
 115 120 125
 Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
 130 135 140
 Cys Gln Ser Ile Ile Ser Thr Leu Thr
 145 150

<210> 55
 <211> 125
 <212> PRT
 <213> Homo sapiens

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<400> 55

Met Lys Lys Ser Gly Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val
 1 5 10 15

Leu Ile Gly Val Gln Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser
 20 25 30

Cys Ile Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp
 35 40 45

Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile
 50 55 60

Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala
 65 70 75 80

Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys
 85 90 95

Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys
 100 105 110

Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr
 115 120 125

<210> 56

<211> 210

<212> PRT

<213> Homo sapiens

<400> 56

Met Leu Pro Leu Pro Ser Cys Ser Leu Pro Ile Leu Leu Leu Phe Leu
 1 5 10 15

Leu Pro Ser Val Pro Ile Glu Ser Gln Pro Pro Pro Ser Thr Leu Pro
 20 25 30

Pro Phe Leu Ala Pro Glu Trp Asp Leu Leu Ser Pro Arg Val Val Leu
 35 40 45

Ser Arg Gly Ala Pro Ala Gly Pro Pro Leu Leu Phe Leu Leu Glu Ala
 50 55 60

Gly Ala Phe Arg Glu Ser Ala Gly Ala Pro Ala Asn Arg Ser Arg Arg
 65 70 75 80

Gly Val Ser Glu Thr Ala Pro Ala Ser Arg Arg Gly Glu Leu Ala Val
 85 90 95

Cys Asp Ala Val Ser Gly Trp Val Thr Asp Arg Arg Thr Ala Val Asp
 100 105 110

Leu Arg Gly Arg Glu Val Glu Val Leu Gly Glu Val Pro Ala Ala Gly
 115 120 125

Gly Ser Pro Leu Arg Gln Tyr Phe Phe Glu Thr Arg Cys Lys Ala Asp
 130 135 140

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Asn Ala Glu Glu Gly Gly Pro Gly Ala Gly Gly Gly Gly Cys Arg Gly
 145 150 155 160
 Val Asp Arg Arg His Trp Val Ser Glu Cys Lys Ala Lys Gln Ser Tyr
 165 170 175
 Val Arg Ala Leu Thr Ala Asp Ala Gln Gly Arg Val Gly Trp Arg Trp
 180 185 190
 Ile Arg Ile Asp Thr Ala Cys Val Cys Thr Leu Leu Ser Arg Thr Gly
 195 200 205
 Arg Ala
 210

<210> 57
 <211> 259
 <212> PRT
 <213> Homo sapiens

<400> 57
 Met Ser Glu Val Pro Val Ala Arg Val Trp Leu Val Leu Leu Leu Leu
 1 5 10 15
 Thr Val Gln Val Gly Val Thr Ala Gly Ala Pro Trp Gln Cys Ala Pro
 20 25 30
 Cys Ser Ala Glu Lys Leu Ala Leu Cys Pro Pro Val Ser Ala Ser Cys
 35 40 45
 Ser Glu Val Thr Arg Ser Ala Gly Cys Gly Cys Cys Pro Met Cys Ala
 50 55 60
 Leu Pro Leu Gly Ala Ala Cys Gly Val Ala Thr Ala Arg Cys Ala Arg
 65 70 75 80
 Gly Leu Ser Cys Arg Ala Leu Pro Gly Glu Gln Gln Pro Leu His Ala
 85 90 95
 Leu Thr Arg Gly Gln Gly Ala Cys Val Gln Glu Ser Asp Ala Ser Ala
 100 105 110
 Pro His Ala Ala Glu Ala Gly Ser Pro Glu Ser Pro Glu Ser Thr Glu
 115 120 125
 Ile Thr Glu Glu Glu Leu Leu Asp Asn Phe His Leu Met Ala Pro Ser
 130 135 140
 Glu Glu Asp His Ser Ile Leu Trp Asp Ala Ile Ser Thr Tyr Asp Gly
 145 150 155 160
 Ser Lys Ala Leu His Val Thr Asn Ile Lys Lys Trp Lys Glu Pro Cys
 165 170 175
 Arg Ile Glu Leu Tyr Arg Val Val Glu Ser Leu Ala Lys Ala Gln Glu
 180 185 190

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[illegible]

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<210> 58
<211> 107
<212> PRT
<213> Homo sapiens
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<400> 58															
Met	Ala	Arg	Ala	Thr	Leu	Ser	Ala	Ala	Pro	Ser	Asn	Pro	Arg	Leu	Leu
1				5					10					15	
Arg	Val	Ala	Leu	Leu	Leu	Leu	Leu	Leu	Val	Ala	Ala	Ser	Arg	Arg	Ala
			20					25					30		
Ala	Gly	Ala	Pro	Leu	Ala	Thr	Glu	Leu	Arg	Cys	Gln	Cys	Leu	Gln	Thr
		35					40					45			
Leu	Gln	Gly	Ile	His	Leu	Lys	Asn	Ile	Gln	Ser	Val	Lys	Val	Lys	Ser
	50					55					60				
Pro	Gly	Pro	His	Cys	Ala	Gln	Thr	Glu	Val	Ile	Ala	Thr	Leu	Lys	Asn
65					70					75					80
Gly	Gln	Lys	Ala	Cys	Leu	Asn	Pro	Ala	Ser	Pro	Met	Val	Lys	Lys	Ile
				85					90					95	
Ile	Glu	Lys	Met	Leu	Lys	Asn	Gly	Lys	Ser	Asn					
			100					105							

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<210> 59
<211> 455
<212> PRT
<213> Homo sapiens
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<400> 59
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
1 5 10 15
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30

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His	Leu	Gly 35	Asp	Arg	Glu	Lys	Arg 40	Asp	Ser	Val	Cys	Pro 45	Gln	Gly	Lys
Tyr	Ile 50	His	Pro	Gln	Asn	Asn 55	Ser	Ile	Cys	Cys	Thr 60	Lys	Cys	His	Lys
Gly 65	Thr	Tyr	Leu	Tyr	Asn 70	Asp	Cys	Pro	Gly	Pro 75	Gly	Gln	Asp	Thr	Asp 80
Cys	Arg	Glu	Cys	Glu 85	Ser	Gly	Ser	Phe	Thr 90	Ala	Ser	Glu	Asn	His 95	Leu
Arg	His	Cys	Leu 100	Ser	Cys	Ser	Lys	Cys 105	Arg	Lys	Glu	Met	Gly 110	Gln	Val
Glu	Ile	Ser 115	Ser	Cys	Thr	Val	Asp 120	Arg	Asp	Thr	Val	Cys 125	Gly	Cys	Arg
Lys	Asn 130	Gln	Tyr	Arg	His	Tyr 135	Trp	Ser	Glu	Asn	Leu 140	Phe	Gln	Cys	Phe
Asn 145	Cys	Ser	Leu	Cys	Leu 150	Asn	Gly	Thr	Val	His 155	Leu	Ser	Cys	Gln	Glu 160
Lys	Gln	Asn	Thr 165	Val	Cys	Thr	Cys	His	Ala 170	Gly	Phe	Phe	Leu	Arg 175	Glu
Asn	Glu	Cys	Val 180	Ser	Cys	Ser	Asn	Cys 185	Lys	Lys	Ser	Leu	Glu 190	Cys	Thr
Lys	Leu	Cys 195	Leu	Pro	Gln	Ile	Glu 200	Asn	Val	Lys	Gly	Thr 205	Glu	Asp	Ser
Gly	Thr 210	Thr	Val	Leu	Leu	Pro 215	Leu	Val	Ile	Phe	Phe 220	Gly	Leu	Cys	Leu
Leu 225	Ser	Leu	Leu	Phe	Ile 230	Gly	Leu	Met	Tyr	Arg 235	Tyr	Gln	Arg	Trp	Lys 240
Ser	Lys	Leu	Tyr	Ser 245	Ile	Val	Cys	Gly	Lys 250	Ser	Thr	Pro	Glu	Lys 255	Glu
Gly	Glu	Leu	Glu 260	Gly	Thr	Thr	Thr	Lys 265	Pro	Leu	Ala	Pro	Asn 270	Pro	Ser
Phe	Ser	Pro 275	Thr	Pro	Gly	Phe	Thr 280	Pro	Thr	Leu	Gly	Phe 285	Ser	Pro	Val
Pro	Ser 290	Ser	Thr	Phe	Thr	Ser 295	Ser	Ser	Thr	Tyr	Thr 300	Pro	Gly	Asp	Cys
Pro 305	Asn	Phe	Ala	Ala	Pro 310	Arg	Arg	Glu	Val	Ala 315	Pro	Pro	Tyr	Gln	Gly 320
Ala	Asp	Pro	Ile 325	Leu	Ala	Thr	Ala	Leu	Ala 330	Ser	Asp	Pro	Ile	Pro 335	Asn

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Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
 340 345 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
 355 360 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
 370 375 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
 385 390 395 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
 405 410 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
 420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
 435 440 445

Pro Ala Pro Ser Leu Leu Arg
 450 455

<210> 60
 <211> 235
 <212> PRT
 <213> Homo sapiens

<400> 60
 Met Thr Val Leu Ala Pro Ala Trp Ser Pro Thr Thr Tyr Leu Leu Leu
 1 5 10 15

Leu Leu Leu Leu Ser Ser Gly Leu Ser Gly Thr Gln Asp Cys Ser Phe
 20 25 30

Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
 35 40 45

Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
 50 55 60

Gln Asp Glu Glu Leu Cys Gly Ala Leu Trp Arg Leu Val Leu Ala Gln
 65 70 75 80

Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
 85 90 95

Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
 100 105 110

Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 115 120 125

Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 130 135 140

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Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
 145 150 155 160

Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala
 165 170 175

Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu Leu Leu Leu Leu Leu
 180 185 190

Pro Val Gly Leu Leu Leu Leu Ala Ala Ala Trp Cys Leu His Trp Gln
 195 200 205

Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly Glu Gln Val Pro Pro Val
 210 215 220

Pro Ser Pro Gln Asp Leu Leu Leu Val Glu His
 225 230 235

<210> 61
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 61
 Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu
 1 5 10 15

Gly Leu Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro
 20 25 30

Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr
 35 40 45

Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile
 50 55 60

Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser
 65 70 75 80

Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala
 85 90 95

Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu
 100 105 110

Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr
 115 120 125

Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln
 130 135 140

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn
 145 150 155 160

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu
 165 170 175

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Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His
180 185 190

Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala
195 200 205

Leu Arg Gln Met
210

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<210> 62
<211> 99
<212> PRT
<213> Homo sapiens
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<400> 62
Met Lys Val Ser Ala Ala Leu Leu Cys Leu Leu Leu Ile Ala Ala Thr
  1             5             10             15
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Phe Ile Pro Gln Gly Leu Ala Gln Pro Asp Ala Ile Asn Ala Pro Val
20 25 30

Thr Cys Cys Tyr Asn Phe Thr Asn Arg Lys Ile Ser Val Gln Arg Leu
35 40 45

Ala Ser Tyr Arg Arg Ile Thr Ser Ser Lys Cys Pro Lys Glu Ala Val
50 55 60

Ile Phe Lys Thr Ile Val Ala Lys Glu Ile Cys Ala Asp Pro Lys Gln
65 70 75 80

Lys Trp Val Gln Asp Ser Met Asp His Leu Asp Lys Gln Thr Gln Thr
85 90 95

Pro Lys Thr

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<210> 63
<211> 233
<212> PRT
<213> Homo sapiens
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<400> 63
Met Ser Thr Glu Ser Met Ile Arg Asp Val Glu Leu Ala Glu Glu Ala
1 5 10 15

Leu Pro Lys Lys Thr Gly Gly Pro Gln Gly Ser Arg Arg Cys Leu Phe
20 25 30

Leu Ser Leu Phe Ser Phe Leu Ile Val Ala Gly Ala Thr Thr Leu Phe
35 40 45

Cys Leu Leu His Phe Gly Val Ile Gly Pro Gln Arg Glu Glu Phe Pro
50 55 60

Arg Asp Leu Ser Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser
65 70 75 80

Ser	Arg	Thr	Pro	Ser 85	Asp	Lys	Pro	Val	Ala 90	His	Val	Val	Ala	Asn 95	Pro
Gln	Ala	Glu	Gly 100	Gln	Leu	Gln	Trp	Leu 105	Asn	Arg	Arg	Ala	Asn 110	Ala	Leu
Leu	Ala	Asn 115	Gly	Val	Glu	Leu	Arg 120	Asp	Asn	Gln	Leu	Val 125	Val	Pro	Ser
Glu	Gly 130	Leu	Tyr	Leu	Ile	Tyr 135	Ser	Gln	Val	Leu	Phe 140	Lys	Gly	Gln	Gly
Cys 145	Pro	Ser	Thr	His	Val 150	Leu	Leu	Thr	His	Thr 155	Ile	Ser	Arg	Ile	Ala 160
Val	Ser	Tyr	Gln	Thr 165	Lys	Val	Asn	Leu	Leu	Ser	Ala	Ile	Lys	Ser 175	Pro
Cys	Gln	Arg	Glu 180	Thr	Pro	Glu	Gly	Ala 185	Glu	Ala	Lys	Pro	Trp 190	Tyr	Glu
Pro	Ile	Tyr 195	Leu	Gly	Gly	Val	Phe 200	Gln	Leu	Glu	Lys	Gly 205	Asp	Arg	Leu
Ser	Ala 210	Glu	Ile	Asn	Arg	Pro 215	Asp	Tyr	Leu	Asp	Phe 220	Ala	Glu	Ser	Gly
Gln 225	Val	Tyr	Phe	Gly	Ile 230	Ile	Ala	Leu							

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<400> 64
Met Ala Pro Leu Lys Met Leu Ala Leu Val Thr Leu Leu Leu Gly Ala
  1              5              10              15
Ser Leu Gln His Ile His Ala Ala Arg Gly Thr Asn Val Gly Arg Glu
              20              25              30
Cys Cys Leu Glu Tyr Phe Lys Gly Ala Ile Pro Leu Arg Lys Leu Lys
      35              40              45
Thr Trp Tyr Gln Thr Ser Glu Asp Cys Ser Arg Asp Ala Ile Val Phe
  50              55              60
Val Thr Val Gln Gly Arg Ala Ile Cys Ser Asp Pro Asn Asn Lys Arg
  65              70              75              80
Val Lys Asn Ala Val Lys Tyr Leu Gln Ser Leu Glu Arg Ser
      85              90

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<210> 65

<211> 267

<212> PRT

<213> Homo sapiens

<400> 65

Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
 1 5 10 15

Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
 20 25 30

Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
 35 40 45

Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
 50 55 60

Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
 65 70 75 80

Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
 85 90 95

Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
 100 105 110

Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
 115 120 125

Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
 130 135 140

Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
 145 150 155 160

Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
 165 170 175

Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
 180 185 190

Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
 195 200 205

Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
 210 215 220

Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
 225 230 235 240

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
 245 250 255

Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
 260 265

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<210> 66

<211> 707

<212> PRT

<213> Homo sapiens

<400> 66

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Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
  1                               10                      15

Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
      20                      25                      30

Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
      35                      40                      45

Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
      50                      55                      60

Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
      65                      70                      75                      80

Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
      85                      90                      95

Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
      100                      105                      110

Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
      115                      120                      125

Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
      130                      135                      140

Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
      145                      150                      155                      160

Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
      165                      170                      175

Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
      180                      185                      190

Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
      195                      200                      205

Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
      210                      215                      220

Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
      225                      230                      235                      240

Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
      245                      250                      255

Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
      260                      265                      270

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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
 275 280 285
 Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
 290 295 300
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
 305 310 315 320
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
 325 330 335
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
 340 345 350
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
 355 360 365
 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
 370 375 380
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
 385 390 395 400
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
 405 410 415
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
 420 425 430
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
 435 440 445
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
 450 455 460
 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
 465 470 475 480
 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
 485 490 495
 Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
 500 505 510
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
 515 520 525
 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
 530 535 540
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
 545 550 555 560
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
 565 570 575

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Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
 580 585 590
 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
 595 600 605
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
 610 615 620
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
 625 630 635 640
 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
 645 650 655
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
 660 665 670
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
 675 680 685
 Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
 690 695 700
 Pro Glu Asp
 705

<210> 67
 <211> 167
 <212> PRT
 <213> Homo sapiens

<400> 67
 Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
 1 5 10 15
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 20 25 30
 Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
 35 40 45
 Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
 50 55 60
 Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
 65 70 75 80
 Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
 85 90 95
 Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
 100 105 110
 Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
 115 120 125

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Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
 130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
 145 150 155 160

Leu Asp Leu Ser Pro Gly Cys
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<210> 68
 <211> 2619
 <212> DNA
 <213> Homo sapiens

<400> 68
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 aagcctcagc cattcactgc cccagctct tctccccagg tgtgttgggg ccttggctcc 2520

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cctgctgaag gtggggattg cccatccatc tgcttacaat tccctgctgt cgtcttagca 2580
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<210> 69
 <211> 711
 <212> PRT
 <213> Homo sapiens

<400> 69
 Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
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 20 25 30
 Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
 35 40 45
 Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60
 Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80
 Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95
 Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110
 Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125
 Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140
 Trp Asn Val Pro Thr Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160
 Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175
 Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu
 180 185 190
 Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205
 Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220
 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255

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Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270
 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
 275 280 285
 Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300
 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320
 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335
 Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350
 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400
 Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
 405 410 415
 Gly Tyr Val Tyr Thr Ala Cys Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510
 Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525
 Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540
 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560

Asp	Val	Ala	Phe	Val 565	Lys	Asp	Val	Thr	Val 570	Leu	Gln	Asn	Thr	Asp	Gly
Asn	Asn	Asn	Glu 580	Ala	Trp	Ala	Lys	Asp 585	Leu	Lys	Leu	Ala	Asp 590	Phe	Ala
Leu	Leu	Cys 595	Leu	Asp	Gly	Lys	Arg 600	Lys	Pro	Val	Thr	Glu 605	Ala	Arg	Ser
Cys	His 610	Leu	Ala	Met	Ala	Pro 615	Asn	His	Ala	Val	Val 620	Ser	Arg	Met	Asp
Lys 625	Val	Glu	Arg	Leu	Lys 630	Gln	Val	Leu	Leu	His 635	Gln	Gln	Ala	Lys	Phe 640
Gly	Arg	Asn	Gly	Ser 645	Asp	Cys	Pro	Asp	Lys 650	Phe	Cys	Leu	Phe	Gln 655	Ser
Glu	Thr	Lys	Asn 660	Leu	Leu	Phe	Asn	Asp 665	Asn	Thr	Glu	Cys	Leu 670	Ala	Arg
Leu	His	Gly 675	Lys	Thr	Thr	Tyr	Glu 680	Lys	Tyr	Leu	Gly	Pro 685	Gln	Tyr	Val
Ala	Gly 690	Ile	Thr	Asn	Leu	Lys 695	Lys	Cys	Ser	Thr	Ser 700	Pro	Leu	Leu	Glu
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<400> 71
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1 5 10 15

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His Ala Gln Ala Gln Asp Ser Thr Ser Asp Leu Ile Pro Ala Pro Pro
 20 25 30
 Leu Ser Lys Val Pro Leu Gln Gln Asn Phe Gln Asp Asn Gln Phe Gln
 35 40 45
 Gly Lys Trp Tyr Val Val Gly Leu Ala Gly Asn Ala Ile Leu Arg Glu
 50 55 60
 Asp Lys Asp Pro Gln Lys Met Tyr Ala Thr Ile Tyr Glu Leu Lys Glu
 65 70 75 80
 Asp Lys Ser Tyr Asn Val Thr Ser Val Leu Phe Arg Lys Lys Lys Cys
 85 90 95
 Asp Tyr Trp Ile Arg Thr Phe Val Pro Gly Cys Gln Pro Gly Glu Phe
 100 105 110
 Thr Leu Gly Asn Ile Lys Ser Tyr Pro Gly Leu Thr Ser Tyr Leu Val
 115 120 125
 Arg Val Val Ser Thr Asn Tyr Asn Gln His Ala Met Val Phe Phe Lys
 130 135 140
 Lys Val Ser Gln Asn Arg Glu Tyr Phe Lys Ile Thr Leu Tyr Gly Arg
 145 150 155 160
 Thr Lys Glu Leu Thr Ser Glu Leu Lys Glu Asn Phe Ile Arg Phe Ser
 165 170 175
 Lys Tyr Leu Gly Leu Pro Glu Asn His Ile Val Phe Pro Val Pro Ile
 180 185 190
 Asp Gln Cys Ile Asp Gly
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<210> 72

<211> 2334

<212> DNA

<213> Homo sapiens

<400> 72

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ccttatcgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggctc ttgaggagcc 1740
gctctccaag aagcttttct tcttctctgg gcgccagggtg tgggtgtaca caggcgcgctc 1800
ggtgctgggc ccgaggcgctc tggacaagct gggcctggga gccgacgtgg cccaggtgac 1860
cggggccctc cggagtggca gggggaagat gctgctgttc agcgggcggc gcctctggag 1920
gttcgacgtg aaggcgcgca tggtgatcc cgggagcgcc agcaggtgg accgatgtt 1980
ccccgggggtg cctttggaca cgcacgacgt cttccagtac cgagagaaaag cctatttctg 2040
ccaggaccgc ttctactggc gcgtgagttc ccgagtgag ttgaaccagg tggaccaagt 2100
gggtacgtg acctatgaca tctgcatgtg cctgaggac tagggctccc gtccgtctt 2160
gcagtgccat gtaaatcccc actgggacca accctgggga aggagccagt ttgccgata 2220
caactggta ttctgttctg gaggaagggt aggagtgagg gtgggctggg ccctctcttc 2280
tcacctttgt tttttgttg agtggttcta ataaacttgg attctctaac cttt 2334

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<210> 73

<211> 2116

<212> DNA

<213> Homo sapiens

<400> 73

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cggttctcca agcaccacgc atcctgctag acgcgcgcgc caccgacgga ggggacatgg 60
gcagagcaat ggtggccagg ctggggctgg ggctgctgct gctggcactg ctctaccca 120
cgcagattta ttccagtga aacaacaactg gaacttcaag taactcctcc cagagtactt 180
ccaactctgg gttggcccca aatccaacta atgccaccac caaggcggct ggtggtgcc 240
tgcagtcaac agccagtctc ttctgtgtct cactctctct tctgcatctc tactcttaag 300
agactcaggc caagaaacgt cttctaaatt tccccctctt ctaaacccaa tccaaatggc 360
gtctggaag ccaatgtggc aaggaaaaac aggtcttcat cgaatctact aattccacac 420
cttttattga cacagaaaat gttgagaatc ccaaatttga ttgatttgaa gaacatgtga 480
gaggtttgac tagatgatga atgccaatat taaatctgct ggagtttcat gtacaagatg 540
aaggagaggc aacatccaaa atagttaaga catgatttcc ttgaatgtgg cttgagaaat 600
atggacactt aatactacct tgaaaataag aatagaaata aaggatggga ttgtggaatg 660
gagattcagt ttctattggg tcattaattc tataaggcca taaaacagg aatataaaaa 720
gcttccatcg atctatttat atgtacatga gaaggaaatc ccagggtgta ctgtaattcc 780
tcaacgtatt gtttcgacgg cactaattta atgcccgat atctctagatg aatgtttaca 840
ttgttgagct attgctgttc tcttggaac tgaactcact ttcctcctga ggctttggat 900
ttgacattgc atttgacctt ttaggtagta attgacatgt gccagggcaa tgatgaatga 960
gaatctaccc cagatccaag catcctgagc aactcttgat tatccatatt gactcaaatg 1020
gtaggcattt cctatcacct gtttccattc aacaagagca ctacattctt ttagctaaac 1080
ggattccaaa gagtagaatt gcattgacca cgactaattt caaaatgctt tttattatta 1140
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tcagtgtacc atttgccctc cgggctcaag cgattctcct gcctcagcct cccaagtagc 1260
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tttatttctg catatgtttg aatacttttt acaattttaa aaaatgatct gttttgaagg 1500
caaaattgca aatcttgaaa ttaagaaggc aaaatgtaaa ggagtcaaac tataaatcaa 1560

```

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```

gtatttgga agtgaagact ggaagctaatt ttgcataaat tcacaaactt ttatactctt 1620
tctgtatata catttttttt ctttaaaaaa caactatgga tcagaatagc aacatttaga 1680
acactttttg ttatcagtc atatttttag atagtttagaa cctggtccta agcctaaaag 1740
tgggcttgat tctgcagtaa atctttttaca actgcctcga cacacataaa ctttttttaa 1800
aatagacact ccccgaaagtc ttttgtttgt atggtcacac actgatgctt agatgttcca 1860
gtaatcta atggccacag tagtcttgat gaccaaagtc ctttttttcc atcttttagaa 1920
aactacatgg gaacaaacag atcgaacagt tttgaagcta ctgtgtgtgt gaatgaacac 1980
tcttgcttta ttccagaatg ctgtacatct attttggtt gtatattgtg gttgtgtatt 2040
tacgctttga ttcataagtaa cttcttatgg aattgatttg cattgaacga caaactgtaa 2100
ataaaaagaa acggtg 2116

```

<210> 74

<211> 80

<212> PRT

<213> Homo sapiens

<400> 74

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Met Gly Arg Ala Met Val Ala Arg Leu Gly Leu Gly Leu Leu Leu Leu
  1             5             10             15
Ala Leu Leu Leu Pro Thr Gln Ile Tyr Ser Ser Glu Thr Thr Thr Gly
          20             25             30
Thr Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro
          35             40             45
Asn Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser
          50             55             60
Thr Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser
          65             70             75             80

```

<210> 75

<211> 1864

<212> DNA

<213> Homo sapiens

<400> 75

```

gtgggtttttc ggatcatgtc tgggtggctcc gcggtattata acagagaaca tggcggtccca 60
gaggggaatgg accccgatgg tgtcatcgag agcaactgga atgagattgt tgataacttt 120
gatgatatga atttaaagga gtctctcctt cgtggcatct atgcttacgg ttttgagaag 180
ccttccgcta ttcagcagag agctattatt ccctgtatta aagggtatga tgtgattgct 240
caagctcagt cagggtactgg caagacagcc acatttgcta tttccatcct gcaacagttg 300
gagattgagt tcaaggagac ccaagcacta gtattggccc ccaccagaga actgggtcaa 360
cagatccaaa aggttaattct ggcacttggg gactatatgg gagccacttg tcatgcctgc 420
attggtggaa caaatgttcg aatgaaatg caaaaactgc aggctgaagc accacatatt 480
gttggtggta caccggggag agtgtttgat atgttaaaca gaagatacct ttctccaaaa 540
tggatcaaaa tgtttgtttt ggatgaagca gatgaaatgt tgagccgtgg ttttaaggat 600
caaatctatg agattttcca aaaactaaac acaagtattc aggttggtgt tgcttctgcc 660
acaatgccaa ctgatgtgtt ggaagtgacc aaaaaattca tgagagatcc aattcgaatt 720
ctggtgaaaa aggaagaatt gacccttgaa ggaatcaaac agttttatat taatgttgag 780
agagaggaat ggaagtggga tacactttgt gacttgtacg agacactgac cattacacag 840
gctgttattt ttctcaatac gaggcgcaag gtggactggc tgactgagaa gatgcatgcc 900

```


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```

agagacttca cagtttctgc tctgcatggt gacatggacc agaaggagag agatgtttatc 960
atgaggggaat tccggtcagg gtcaagtcgt gttctgatca ctactgactt gttggctcgc 1020
gggattgatg tgcaacaagt gtctttgggt ataaattatg atctacctac caatcgtgaa 1080
aactatattc acagaattgg cagagggggt cgatttgga ggaaagggtg ggctataaac 1140
tttgttactg aagaagacaa gaggattcct cgtgacattg agactttcta caatactaca 1200
gtggaggaga tgcccatgaa tgtggctgac cttatttaat tcctgggatg agagttttgg 1260
atgcagtgct cgctgttgct gaataggcga tcacaacgtg cattgtgctt ctttctttgg 1320
gaatatttga atcttgtctc aatgctcata acggatcaga aatacagatt ttgatagcaa 1380
agcgacgtta gtcgtgagct cttgtgagga aagtcattgg ctttatcctc tttagagtta 1440
gactgttggg gtgggtataa aagatggggt ctgtaaaatc tttctttctt agaaatttat 1500
ttcctagttc ttagaaaatg gttgtattag atgttctcta tcatttaata atatacttgt 1560
ggactaaaag atataagtcg tgtataaaat cagccaatta tgttaaaacta gcatactctgc 1620
ctttattgtg tttgtcatta gcctgagtag aaaggccttt aaaatttttt tagaaagcat 1680
ttgaatgcat tttgtttggg attgtattta ttcaataaag tatttaatta gtgctaagt 1740
tgaactggac cctgttgcta agccccagca agcaatccta ggtagggttt aatccccagt 1800
aaaattgcc aattgcacat gtcttaatga agtttgaatg ttaaataaat tgtatattca 1860
cttt

```

<210> 76

<211> 407

<212> PRT

<213> Homo sapiens

<400> 76

```

Met Ser Gly Gly Ser Ala Asp Tyr Asn Arg Glu His Gly Gly Pro Glu
  1             5             10             15

```

```

Gly Met Asp Pro Asp Gly Val Ile Glu Ser Asn Trp Asn Glu Ile Val
          20             25             30

```

```

Asp Asn Phe Asp Asp Met Asn Leu Lys Glu Ser Leu Leu Arg Gly Ile
          35             40             45

```

```

Tyr Ala Tyr Gly Phe Glu Lys Pro Ser Ala Ile Gln Gln Arg Ala Ile
          50             55             60

```

```

Ile Pro Cys Ile Lys Gly Tyr Asp Val Ile Ala Gln Ala Gln Ser Gly
          65             70             75             80

```

```

Thr Gly Lys Thr Ala Thr Phe Ala Ile Ser Ile Leu Gln Gln Leu Glu
          85             90             95

```

```

Ile Glu Phe Lys Glu Thr Gln Ala Leu Val Leu Ala Pro Thr Arg Glu
          100            105            110

```

```

Leu Ala Gln Gln Ile Gln Lys Val Ile Leu Ala Leu Gly Asp Tyr Met
          115            120            125

```

```

Gly Ala Thr Cys His Ala Cys Ile Gly Gly Thr Asn Val Arg Asn Glu
          130            135            140

```

```

Met Gln Lys Leu Gln Ala Glu Ala Pro His Ile Val Val Gly Thr Pro
          145            150            155            160

```

```

Gly Arg Val Phe Asp Met Leu Asn Arg Arg Tyr Leu Ser Pro Lys Trp
          165            170            175

```

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Ile Lys Met Phe Val Leu Asp Glu Ala Asp Glu Met Leu Ser Arg Gly
 180 185 190
 Phe Lys Asp Gln Ile Tyr Glu Ile Phe Gln Lys Leu Asn Thr Ser Ile
 195 200 205
 Gln Val Val Phe Ala Ser Ala Thr Met Pro Thr Asp Val Leu Glu Val
 210 215 220
 Thr Lys Lys Phe Met Arg Asp Pro Ile Arg Ile Leu Val Lys Lys Glu
 225 230 235 240
 Glu Leu Thr Leu Glu Gly Ile Lys Gln Phe Tyr Ile Asn Val Glu Arg
 245 250 255
 Glu Glu Trp Lys Leu Asp Thr Leu Cys Asp Leu Tyr Glu Thr Leu Thr
 260 265 270
 Ile Thr Gln Ala Val Ile Phe Leu Asn Thr Arg Arg Lys Val Asp Trp
 275 280 285
 Leu Thr Glu Lys Met His Ala Arg Asp Phe Thr Val Ser Ala Leu His
 290 295 300
 Gly Asp Met Asp Gln Lys Glu Arg Asp Val Ile Met Arg Glu Phe Arg
 305 310 315 320
 Ser Gly Ser Ser Arg Val Leu Ile Thr Thr Asp Leu Leu Ala Arg Gly
 325 330 335
 Ile Asp Val Gln Gln Val Ser Leu Val Ile Asn Tyr Asp Leu Pro Thr
 340 345 350
 Asn Arg Glu Asn Tyr Ile His Arg Ile Gly Arg Gly Gly Arg Phe Gly
 355 360 365
 Arg Lys Gly Val Ala Ile Asn Phe Val Thr Glu Glu Asp Lys Arg Ile
 370 375 380
 Leu Arg Asp Ile Glu Thr Phe Tyr Asn Thr Thr Val Glu Glu Met Pro
 385 390 395 400
 Met Asn Val Ala Asp Leu Ile
 405

<210> 77
 <211> 1670
 <212> DNA
 <213> Homo sapiens

<400> 77
 cggcacgagg caagtgacgc cgagggcctg agtgctccag tagccaccgc atctggagaa 60
 ccagcgggta ccatggaggg gatcagtata tacacttcag ataactacac cgaggaaatg 120
 ggctcagggg actatgactc catgaaggaa ccctgtttcc gtgaagaaaa tgctaatttc 180
 aataaaatct tctgcccac catctactcc atcatcttct taactggcat tgtgggcaat 240
 ggattgggtca tcttggtcat gggttaccag aagaaactga gaagcatgac ggacaagtac 300
 aggctgcacc tgtcagtggc cgacctctc tttgtcatca cgcttcocctt ctgggcagtt 360

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```

gatgccgtgg caaactggta ctttgggaac ttctatgca aggcagtcca tgtcatctac 420
acagtcaacc tctacagcag tgtcctcatc ctggccttca tcagtctgga ccgctacctg 480
gccatcgctc acgccaccaa cagtcagagg ccaaggaagc tgttggctga aaaggtggtc 540
tatgttggcg tctggatccc tgccctcctg ctgactattc ccgacttcat ctttgccaac 600
gtcagtgagg cagatgacag atatatctgt gaccgcttct accccaatga cttgtgggtg 660
gttgtgttcc agtttcagca catcatgggt ggcccttatcc tgcctgggat tgtcatcctg 720
tcctgtctatt gcattatcat ctccaagctg tcacactcca agggccacca gaagcgcaag 780
gccctcaaga ccacagtcac cctcatcctg gctttcttcg cctgttggct gccttactac 840
attgggatca gcatcgactc cttcatcctc ctggaaatca tcaagcaagg gtgtgagttt 900
gagaacactg tgcacaagtg gatttccatc accgaggccc tagctttctt ccactgttgt 960
ctgaacccca tcctctatgc tttccttgga gccaaattta aaacctctgc ccagcacgca 1020
ctcacctctg tgagcagagg gtccagcctc aagatcctct ccaaaggaaa gcgaggtgga 1080
cattcatctg tttccactga gtctgagttc tcaagttttc actccagcta acacagatgt 1140
aagagacttt tttttatacg ataaataact tttttttaag ttacacattt ttcagatata 1200
aaagactgac caatattgta cagtttttat tgcctgttgg atttttgctc ttgtgtttct 1260
ttagtttttc gtgaaggttt aattgactta tttatataaa ttttttttgt ttcattattga 1320
tgtgtgtcta ggcaggacct gtggccaagt tcttagttgc tgtatgtctc gtggtaggac 1380
tgtagaaaag ggaactgaac attccagagc gtgtagttaa tcacgtaaag ctagaaatga 1440
tccccagctg tttatgcata gataatctct ccattcccggt ggaacgtttt tcctgttctt 1500
aagacgtgat tttgctgtag aagatggcac ttataaccac agcccaaagt ggtatagaaa 1560
tgctggtttt tcagttttca ggagtgggtt gatttcagca cctacagtgt acagtcctgt 1620
attaagttgt taataaaaagt acatgttaaa cttaaaaaaa aaaaaaaaaa 1670

```

<210> 78

<211> 352

<212> PRT

<213> Homo sapiens

<400> 78

```

Met Glu Gly Ile Ser Ile Tyr Thr Ser Asp Asn Tyr Thr Glu Glu Met
  1                      5                      10                      15

```

```

Gly Ser Gly Asp Tyr Asp Ser Met Lys Glu Pro Cys Phe Arg Glu Glu
  .                20                25                30

```

```

Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
  35                40                45

```

```

Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
  50                55                60

```

```

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
  65                70                75                80

```

```

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
  85                90                95

```

```

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
  100               105               110

```

```

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
  115               120               125

```

```

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
  130               135               140

```

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Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val
 145 150 155 160
 Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn
 165 170 175
 Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn
 180 185 190
 Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu
 195 200 205
 Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser
 210 215 220
 Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr
 225 230 235 240
 Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr
 245 250 255
 Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln
 260 265 270
 Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu
 275 280 285
 Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe
 290 295 300
 Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val
 305 310 315 320
 Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly
 325 330 335
 His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser Phe His Ser Ser
 340 345 350

<210> 79
 <211> 1262
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (53)..(53)
 <223> n is a, c, g, or t

<220>
 <221> misc_feature
 <222> (83)..(83)
 <223> n is a, c, g, or t

<220>
 <221> misc_feature

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<222> (897)..(897)
 <223> n is a, c, g, or t

<400> 79
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 cagagccgct ggtagcctaa ggnggggggg cagccaggag aaagccccgc cgctgctcgt 120
 cccgcccctc gggtagccagc accgcccctg ctgcggcggg tgagggggcg ggcggggccg 180
 cggcgtatat aaggctaggc ggggcgccgc tcttttgttt cttgctgcag caacgcgagt 240
 gggagcacca ggatctcggg ctcggaacga gactgcacgg tgacgtgacg gccggggcgg 300
 ggcccagggt gtggtcggat ccggtgcacc gcgggcgcgc aaccgggaca ggcgtttctc 360
 ggaccggacg cagggggccg gaccacgccc tgggaccgag aagaggggtg cggacgcgcc 420
 cagatcctcg gccttggggc tgctcggcag ccttggcgcg agtgccacgt cgagaggcgt 480
 cggcggggag cgcggaaggg gacggcctgc gccaggccc aggtcaagcg ccttggtttg 540
 cccactagga ttgttttaag aaaatggcag acaaaccaga catgggggaa atcgccagct 600
 tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag 660
 agagtgagtg tgcctcggtc tccgcgcccc agcccagccc ctaccctgc tcttccttgc 720
 aaaccactc ctccaccccc caccgcgcg ttgtccccgg tgtggcgcg cccggcactc 780
 tttcagtttc acaaagcgcc ttgtttctcc ccagcccaa gcttccttct aaatcccaca 840
 cctcgtgggtg ctcatcacac cgggaagcac ctcggttgcg ggtggggggg tgcagcnccc 900
 ctccagcgcc ccgttcctgc tcaagccatt gaggcaggaga agcggagtga aatttcctaa 960
 gatcctggag gattttctac ccccgtctc tcggagcacc ccagtcgctg atgtggagaa 1020
 gagccaccct gcaagatgga cacgagtcca caagctgcac tgtgaacctg cgagcccgcg 1080
 ccgatgccac cggcctgtgg tcgtctgaag ggaccccccc ccaatcggac tgccaaattc 1140
 tcggtttgcc ccgggatatt atagaaaatt atttgatga ataataaaaa taaaacacac 1200
 ctcgttggca tggctggcgg tggctctgagt gttttagtta gtatgggtgc agtccactgc 1260
 ag 1262

<210> 80
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 80
 Asp Cys Phe Lys Lys Met Ala Asp Lys Pro Asp Met Gly Glu Ile Ala
 1 5 10 15
 Ser Phe Asp Lys Ala Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn
 20 25 30
 Thr Leu Pro Thr Lys Glu Thr Ile Glu Gln Glu Lys Arg Ser Glu Ile
 35 40 45
 Ser

<210> 81
 <211> 1198
 <212> DNA
 <213> Homo sapiens

<400> 81
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 agctgaggaa gctcttcatt ggagggttga gctttgaaac aactgatgag agcctgagga 120
 gccattttga gcaatgggga acgctcacgg actgtgtggt aatgagagat ccaaacacca 180
 agcgtcttag gggctttggg tttgtcacat atgccactgt ggaggagggt gatgcagcta 240
 tgaatgcaag gccacacaag gtggatggaa gagttgtgga accaaagaga gctgtctcca 300

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```

gagaagattc tcaaagacca ggtgcccact taactgtgaa aaagatattt gttggtggca 360
ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg 420
aagtgattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gcctttgtaa 480
cctttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtgaatg 540
gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca 600
gccaaagagg tgaagtggt tctggaaact ttggtggtgg tctggagggt ggtttcgggtg 660
ggaatgacaa cttcggtcgt ggaggaaact tcagtggtcg tgggtggcttt ggtggcagcc 720
gtggtggtgg tggatatggt ggcagtgggg atggctataa tggatttggc aatgatggaa 780
gcaatttttg aggtggtgga agctacaatg attttgggaa ttacaacaat cagtcttcaa 840
attttggacc catgaaggga ggaaattttg gaggcagaag ctctggcccc tatggcgggtg 900
gaggccaata ctttgcaaaa ccacgaaacc aagtggtgcta tggcgggttc agcagcagca 960
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ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ccttgtgaag 1080
acctttatct gagccactgt acttcgttat cagccatgc agtttacatg agctgtttctg 1140
cagctcgaaa ttccattttg tgaatggggt ttttttttta ataaactgta ttttaactt 1198

```

<210> 82

<211> 320

<212> PRT

<213> Homo sapiens

<400> 82

```

Met Ser Lys Ser Glu Ser Pro Lys Glu Pro Glu Gln Leu Arg Lys Leu
  1              5              10              15

Phe Ile Gly Gly Leu Ser Phe Glu Thr Thr Asp Glu Ser Leu Arg Ser
          20              25              30

His Phe Glu Gln Trp Gly Thr Leu Thr Asp Cys Val Val Met Arg Asp
      35              40              45

Pro Asn Thr Lys Arg Ser Arg Gly Phe Gly Phe Val Thr Tyr Ala Thr
      50              55              60

Val Glu Glu Val Asp Ala Ala Met Asn Ala Arg Pro His Lys Val Asp
      65              70              75              80

Gly Arg Val Val Glu Pro Lys Arg Ala Val Ser Arg Glu Asp Ser Gln
          85              90              95

Arg Pro Gly Ala His Leu Thr Val Lys Lys Ile Phe Val Gly Gly Ile
      100              105              110

Lys Glu Asp Thr Glu Glu His His Leu Arg Asp Tyr Phe Glu Gln Tyr
      115              120              125

Gly Lys Ile Glu Val Ile Glu Ile Met Thr Asp Arg Gly Ser Gly Lys
      130              135              140

Lys Arg Gly Phe Ala Phe Val Thr Phe Asp Asp His Asp Ser Val Asp
      145              150              155              160

Lys Ile Val Ile Gln Lys Tyr His Thr Val Asn Gly His Asn Cys Glu
          165              170              175

Val Arg Lys Ala Leu Ser Lys Gln Glu Met Ala Ser Ala Ser Ser Ser
      180              185              190

```

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Gln Arg Gly Arg Ser Gly Ser Gly Asn Phe Gly Gly Gly Arg Gly Gly
 195 200 205

Gly Phe Gly Gly Asn Asp Asn Phe Gly Arg Gly Gly Asn Phe Ser Gly
 210 215 220

Arg Gly Gly Phe Gly Gly Ser Arg Gly Gly Gly Gly Tyr Gly Gly Ser
 225 230 235 240

Gly Asp Gly Tyr Asn Gly Phe Gly Asn Asp Gly Ser Asn Phe Gly Gly
 245 250 255

Gly Gly Ser Tyr Asn Asp Phe Gly Asn Tyr Asn Asn Gln Ser Ser Asn
 260 265 270

Phe Gly Pro Met Lys Gly Gly Asn Phe Gly Gly Arg Ser Ser Gly Pro
 275 280 285

Tyr Gly Gly Gly Gly Gln Tyr Phe Ala Lys Pro Arg Asn Gln Gly Gly
 290 295 300

Tyr Gly Gly Ser Ser Ser Ser Ser Tyr Gly Ser Gly Arg Arg Phe
 305 310 315 320

<210> 83
 <211> 1125
 <212> DNA
 <213> Homo sapiens

<400> 83
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 ctcttcttct tcgtcctcgg cagcctgac ttctgcttcg gcactctgat cctcatcgac 180
 aagaccagct tcgtgtcctt tgtgggcttg gccttcgtgc ctctgcagat ctgggtccaaa 240
 gtccctggcca tctcaggaat cttcaccatg ggcatcgccc tcctggggtg tgtggggggcc 300
 ctcaaggagc tccgctgcct cctgggacctg tattttggga tgctgctgct cctgtttgcc 360
 acacagatca ccttggaat cctcatctcc actcagcggg ccagctgga gcgaagcttg 420
 cgggacgtcg tagagaaaac catccaaaag tacggcacca accccgagga gaccgcggcc 480
 gaggagagct gggactatgt gcagttccag ctgcgctgct gcggctggca ctaccgcag 540
 gactgggtcc aagtccctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc 600
 tcctgctaca acttgctcggc gaccaacgac tccacaatcc tagataaggt gatcttgccc 660
 cagctcagca ggcttgaca cctggcgagg tccagacaca gtgcagacat ctgcgctgtc 720
 cctgcagaga gccacatcta ccgcgagggc tgcgcgcagg gcctccagaa gtggctgcac 780
 aacaacctta tttccatagt gggcatttgc ctgggcgtcg gcctactcga gctcgggttc 840
 atgacgctct cgatattcct gtgcagaaac ctggaccaag tctacaaccg gctcgtcga 900
 tacggttagg ccccgccctc cccaaagtcc cgccccgccc ccgtcacgtg cgctgggcac 960
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 cattccccctg gggaccacag tggctgcgtg cccctgctgc tgtcacctct cccacgggac 1080
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<210> 84
 <211> 281

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<212> PRT

<213> Homo sapiens

<400> 84

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Met Ser Ala Gln Glu Ser Cys Leu Ser Leu Ile Lys Tyr Phe Leu Phe
  1           5           10           15

Val Phe Asn Leu Phe Phe Phe Val Leu Gly Ser Leu Ile Phe Cys Phe
      20           25           30

Gly Ile Trp Ile Leu Ile Asp Lys Thr Ser Phe Val Ser Phe Val Gly
      35           40           45

Leu Ala Phe Val Pro Leu Gln Ile Trp Ser Lys Val Leu Ala Ile Ser
      50           55           60

Gly Ile Phe Thr Met Gly Ile Ala Leu Leu Gly Cys Val Gly Ala Leu
      65           70           75           80

Lys Glu Leu Arg Cys Leu Leu Gly Leu Tyr Phe Gly Met Leu Leu Leu
      85           90           95

Leu Phe Ala Thr Gln Ile Thr Leu Gly Ile Leu Ile Ser Thr Gln Arg
      100          105          110

Ala Gln Leu Glu Arg Ser Leu Arg Asp Val Val Glu Lys Thr Ile Gln
      115          120          125

Lys Tyr Gly Thr Asn Pro Glu Glu Thr Ala Ala Glu Glu Ser Trp Asp
      130          135          140

Tyr Val Gln Phe Gln Leu Arg Cys Cys Gly Trp His Tyr Pro Gln Asp
      145          150          155          160

Trp Phe Gln Val Leu Ile Leu Arg Gly Asn Gly Ser Glu Ala His Arg
      165          170          175

Val Pro Cys Ser Cys Tyr Asn Leu Ser Ala Thr Asn Asp Ser Thr Ile
      180          185          190

Leu Asp Lys Val Ile Leu Pro Gln Leu Ser Arg Leu Gly His Leu Ala
      195          200          205

Arg Ser Arg His Ser Ala Asp Ile Cys Ala Val Pro Ala Glu Ser His
      210          215          220

Ile Tyr Arg Glu Gly Cys Ala Gln Gly Leu Gln Lys Trp Leu His Asn
      225          230          235          240

Asn Leu Ile Ser Ile Val Gly Ile Cys Leu Gly Val Gly Leu Leu Glu
      245          250          255

Leu Gly Phe Met Thr Leu Ser Ile Phe Leu Cys Arg Asn Leu Asp His
      260          265          270

Val Tyr Asn Arg Leu Ala Arg Tyr Arg
      275          280

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<210> 85
 <211> 1216
 <212> DNA
 <213> Homo sapiens

<400> 85
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 ggtgctgagc tccccactgg ctttggctgg ggacacccga ccatgtttct tgcagcagga 180
 taagtatgag tgtcatttct tcaacgggac ggagcgggtg cggttcctgc acagaggcat 240
 ctataaccaa caggagaacg tgcgcttcga cagcgacgtg ggggagtacc gggcggtgac 300
 ggagctgggg cggcctgacg ctgagtactg gaacagccag aaggacatcc tggagcaggc 360
 gcgggccgcg gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt 420
 gcagcggcga gttgagccta aggtgactgt gtatcctgca aggacccaga ccctgcagca 480
 ccacaacctc ctggtctgct ctgtgaatgg tttctatcca ggcagcattg aagtcagggtg 540
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 cacctgccaa gtggagcacc caagcgtgac gagccctctc acagtggaat ggagagcaca 720
 gtctgaatct gcacagagca agatgctgag tggaaatcggg ggctttgtgc tgggacctgt 780
 cttccttggg gccgggctat tcatctactt caagaatcag aaagggcact ctggacttca 840
 cccaacagga ctgctgagct gaagtgcaga tgaccacatt caagggggaa ccttctgccc 900
 cagctttgca tgatgaaaag ctttctgtct tggctcttat tcttcacaa gagaggactt 960
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 tttagtgtct ccttttacct aaccctacgg cctcccatgc atctgtactc cccctgtgcc 1140
 acaaattggac tacgttatta aatttttctg aagcccagag ttaaaaatca tctgtccacc 1200
 tggcaccaaa gacaaa 1216

<210> 86
 <211> 266
 <212> PRT
 <213> Homo sapiens

<400> 86
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 1 5 10 15
 Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu Ala Gly Asp Thr
 20 25 30
 Arg Pro Cys Phe Leu Gln Gln Asp Lys Tyr Glu Cys His Phe Phe Asn
 35 40 45
 Gly Thr Glu Arg Val Arg Phe Leu His Arg Gly Ile Tyr Asn Gln Gln
 50 55 60
 Glu Asn Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr
 65 70 75 80
 Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile
 85 90 95
 Leu Glu Gln Ala Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr
 100 105 110

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Gly Ala Val Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val
 115 120 125
 Thr Val Tyr Pro Ala Arg Thr Gln Thr Leu Gln His His Asn Leu Leu
 130 135 140
 Val Cys Ser Val Asn Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp
 145 150 155 160
 Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu
 165 170 175
 Ile Gln Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Thr
 180 185 190
 Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser
 195 200 205
 Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Gln Ser Glu Ser Ala
 210 215 220
 Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu Gly Leu Leu
 225 230 235 240
 Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Lys Asn Gln Lys Gly His
 245 250 255
 Ser Gly Leu His Pro Thr Gly Leu Val Ser
 260 265

<210> 87

<211> 1881

<212> DNA

<213> Homo sapiens

<400> 87

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ccctcaggct ggggtccctg tgcggttccc gagcagtttc gggatatgcc ctaccagccg 180
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taccagcgga atcgaatgag atttgccag aggaacctcc gcagagacaa agatcgtcgg 420
aacatgttgc agttcaacct gcagatcctg cctaagagtg ccaaacagaa agagagagaa 480
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gagactgcca atgagccccc tcaagatgaa ggtaattcct tcaattcacc ccgcaacctg 1020
gccatggagg caacctacat caaccacaat ttctcccagc agtgcttgag aatggggaag 1080
gaaagatata acttcccaa cccaaaccgg tttgtggagg acgacatgga taagaatgaa 1140
atgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 1200
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 1260

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atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 1320
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gcccgggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 1440
tctcgggtacc acgtgaaaga ctccctcacgc cacgtcatcc taggcaccca gcagttcaag 1500
cctaataagt ttgccagcca gatcaacctg agcgtggaga atgcctgggg cattttacgc 1560
tgcgtcattg acatctgcat gaagctggag gagggcaaat acctcatcct caaggacccc 1620
aacaagcagg tcatccgtgt ctacagcctc cctgatggca ccttcagctc tgatgaagat 1680
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gtggagctgg agtttgtcct tccaccgaga ctacgagggc ctttgatgct tagtggaatg 1800
tgtgtctaac ttgctctctg acatttagca gatgaaataa aatatatatac tgtttagtct 1860
tttaaaaaaa aaaaaaaaaa a 1881

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<210> 88

<211> 548

<212> PRT

<213> Homo sapiens

<400> 88

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Met Ala Lys Phe Met Thr Pro Val Ile Gln Asp Asn Pro Ser Gly Trp
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Gly Pro Cys Ala Val Pro Glu Gln Phe Arg Asp Met Pro Tyr Gln Pro
             20             25             30

Phe Ser Lys Gly Asp Arg Leu Gly Lys Val Ala Asp Trp Thr Gly Ala
             35             40             45

Thr Tyr Gln Asp Lys Arg Tyr Thr Asn Lys Tyr Ser Ser Gln Phe Gly
             50             55             60

Gly Gly Ser Gln Tyr Ala Tyr Phe His Glu Glu Asp Glu Ser Ser Phe
             65             70             75             80

Gln Leu Val Asp Thr Ala Arg Thr Gln Lys Thr Ala Tyr Gln Arg Asn
             85             90             95

Arg Met Arg Phe Ala Gln Arg Asn Leu Arg Arg Asp Lys Asp Arg Arg
             100            105            110

Asn Met Leu Gln Phe Asn Leu Gln Ile Leu Pro Lys Ser Ala Lys Gln
             115            120            125

Lys Glu Arg Glu Arg Ile Arg Leu Gln Lys Lys Phe Gln Lys Gln Phe
             130            135            140

Gly Val Arg Gln Lys Trp Asp Gln Lys Ser Gln Lys Pro Arg Asp Ser
             145            150            155            160

Ser Val Glu Val Arg Ser Asp Trp Glu Val Lys Glu Glu Met Asp Phe
             165            170            175

Pro Gln Leu Met Lys Met Arg Tyr Leu Glu Val Ser Glu Pro Gln Asp
             180            185            190

Ile Glu Cys Cys Gly Ala Leu Glu Tyr Tyr Asp Lys Ala Phe Asp Arg
             195            200            205

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Ile	Thr	Thr	Arg	Ser	Glu	Lys	Pro	Leu	Arg	Ser	Ile	Lys	Arg	Ile	Phe
210						215					220				
His	Thr	Val	Thr	Thr	Thr	Asp	Asp	Pro	Val	Ile	Arg	Lys	Leu	Ala	Lys
225					230					235					240
Thr	Gln	Gly	Asn	Val	Phe	Ala	Thr	Asp	Ala	Ile	Leu	Ala	Thr	Leu	Met
				245					250					255	
Ser	Cys	Thr	Arg	Ser	Val	Tyr	Ser	Trp	Asp	Ile	Val	Val	Gln	Arg	Val
			260					265					270		
Gly	Ser	Lys	Leu	Phe	Phe	Asp	Lys	Arg	Asp	Asn	Ser	Asp	Phe	Asp	Leu
		275					280					285			
Leu	Thr	Val	Ser	Glu	Thr	Ala	Asn	Glu	Pro	Pro	Gln	Asp	Glu	Gly	Asn
290						295					300				
Ser	Phe	Asn	Ser	Pro	Arg	Asn	Leu	Ala	Met	Glu	Ala	Thr	Tyr	Ile	Asn
305					310					315					320
His	Asn	Phe	Ser	Gln	Gln	Cys	Leu	Arg	Met	Gly	Lys	Glu	Arg	Tyr	Asn
				325					330					335	
Phe	Pro	Asn	Pro	Asn	Pro	Phe	Val	Glu	Asp	Asp	Met	Asp	Lys	Asn	Glu
			340					345					350		
Ile	Ala	Ser	Val	Ala	Tyr	Arg	Tyr	Arg	Arg	Trp	Lys	Leu	Gly	Asp	Asp
		355					360					365			
Ile	Asp	Leu	Ile	Val	Arg	Cys	Glu	His	Asp	Gly	Val	Met	Thr	Gly	Ala
370						375					380				
Asn	Gly	Glu	Val	Ser	Phe	Ile	Asn	Ile	Lys	Thr	Leu	Asn	Glu	Trp	Asp
385					390					395					400
Ser	Arg	His	Cys	Asn	Gly	Val	Asp	Trp	Arg	Gln	Lys	Leu	Asp	Ser	Gln
				405					410					415	
Arg	Gly	Ala	Val	Ile	Ala	Thr	Glu	Leu	Lys	Asn	Asn	Ser	Tyr	Lys	Leu
			420					425					430		
Ala	Arg	Trp	Thr	Cys	Cys	Ala	Leu	Leu	Ala	Gly	Ser	Glu	Tyr	Leu	Lys
		435					440					445			
Leu	Gly	Tyr	Val	Ser	Arg	Tyr	His	Val	Lys	Asp	Ser	Ser	Arg	His	Val
450						455					460				
Ile	Leu	Gly	Thr	Gln	Gln	Phe	Lys	Pro	Asn	Glu	Phe	Ala	Ser	Gln	Ile
465					470					475					480
Asn	Leu	Ser	Val	Glu	Asn	Ala	Trp	Gly	Ile	Leu	Arg	Cys	Val	Ile	Asp
				485					490					495	
Ile	Cys	Met	Lys	Leu	Glu	Glu	Gly	Lys	Tyr	Leu	Ile	Leu	Lys	Asp	Pro
			500					505					510		

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Asn Lys Gln Val Ile Arg Val Tyr Ser Leu Pro Asp Gly Thr Phe Ser
 515 520 525

Ser Asp Glu Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
 530 535 540

Glu Glu Glu Thr
 545

<210> 89
 <211> 670
 <212> DNA
 <213> Homo sapiens

<400> 89
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 gccatgaagt tcctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa 240
 gaccgaccat tcttccttgg gctggtgaag tacatgaact cagggccggt tgtggccatg 300
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 gaagaactgg ttgactacaa gtcttggtgct catgactggg tctatgaata agaggtggac 540
 acaacagcag tctccttcag cagggcgtgg tgtgtccctg gacacagctc ttcattccat 600
 tgacttagag gcaacaggat tgatcattct tttatagagc atatttgcca ataaagcttt 660
 tggaagccgg 670

<210> 90
 <211> 152
 <212> PRT
 <213> Homo sapiens

<400> 90
 Met Ala Asn Leu Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val
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 Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly
 20 25 30
 Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu
 35 40 45
 Lys Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu
 50 55 60
 Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly
 65 70 75 80
 Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro
 85 90 95
 Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val
 100 105 110

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Gly Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys
 115 120 125

Glu Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser
 130 135 140

Cys Ala His Asp Trp Val Tyr Glu
 145 150

<210> 91
 <211> 1097
 <212> DNA
 <213> Homo sapiens

<400> 91
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 ttaagatcat ccaactattg gatgattatc cgaaatgttt catttgtgga gcagacaatg 180
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 tcaactgagat cagggacatg ttgctggcca ataagggtgcc agctgctgcc cgtgctggtg 420
 ccattgcccc atgtgaagtc actgtgccag cccagaacac tggctctcggg cccgagaaga 480
 cctccttttt ccaggcttta ggtatcacca ctaaaatctc caggggcacc attgaaatcc 540
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 cagctaaggt tgaagccaag gaagagtcgg aggagtcgga cgaggatatg ggatttggtc 1020
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 taaaggctta cttcttt 1097

<210> 92
 <211> 317
 <212> PRT
 <213> Homo sapiens

<400> 92
 Met Pro Arg Glu Asp Arg Ala Thr Trp Lys Ser Asn Tyr Phe Leu Lys
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 Ile Ile Gln Leu Leu Asp Asp Tyr Pro Lys Cys Phe Ile Val Gly Ala
 20 25 30
 Asp Asn Val Gly Ser Lys Gln Met Gln Gln Ile Arg Met Ser Leu Arg
 35 40 45
 Gly Lys Ala Val Val Leu Met Gly Lys Asn Thr Met Met Arg Lys Ala
 50 55 60
 Ile Arg Gly His Leu Glu Asn Asn Pro Ala Leu Glu Lys Leu Leu Pro
 65 70 75 80

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His Ile Arg Gly Asn Val Gly Phe Val Phe Thr Lys Glu Asp Leu Thr
 85 90 95
 Glu Ile Arg Asp Met Leu Leu Ala Asn Lys Val Pro Ala Ala Ala Arg
 100 105 110
 Ala Gly Ala Ile Ala Pro Cys Glu Val Thr Val Pro Ala Gln Asn Thr
 115 120 125
 Gly Leu Gly Pro Glu Lys Thr Ser Phe Phe Gln Ala Leu Gly Ile Thr
 130 135 140
 Thr Lys Ile Ser Arg Gly Thr Ile Glu Ile Leu Ser Asp Val Gln Leu
 145 150 155 160
 Ile Lys Thr Gly Asp Lys Val Gly Ala Ser Glu Ala Thr Leu Leu Asn
 165 170 175
 Met Leu Asn Ile Ser Pro Phe Ser Phe Gly Leu Val Ile Gln Gln Val
 180 185 190
 Phe Asp Asn Gly Ser Ile Tyr Asn Pro Glu Val Leu Asp Ile Thr Glu
 195 200 205
 Glu Thr Leu His Ser Arg Phe Leu Glu Gly Val Arg Asn Val Ala Ser
 210 215 220
 Val Cys Leu Gln Ile Gly Tyr Pro Thr Val Ala Ser Val Pro His Ser
 225 230 235 240
 Ile Ile Asn Gly Tyr Lys Arg Val Leu Ala Leu Ser Val Glu Thr Asp
 245 250 255
 Tyr Thr Phe Pro Leu Ala Glu Lys Val Lys Ala Phe Leu Ala Asp Pro
 260 265 270
 Ser Ala Phe Val Ala Ala Ala Pro Val Ala Ala Ala Thr Thr Ala Ala
 275 280 285
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 290 295 300
 Glu Glu Ser Asp Glu Asp Met Gly Phe Gly Leu Phe Asp
 305 310 315

<210> 93

<211> 6711

<212> DNA

<213> Homo sapiens

<400> 93

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ccgaggggggt agctgggact acaggtgcgc accaccatgc ccagctaatt ttgtattttt 240
cgtagagatg gggtttcacc atgttgcca ggctggctct gaactcctga cctcaggtga 300
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 Gly Asp Phe Thr Arg His Asn Gly Thr Gly Gly Lys Ser Ile Tyr Gly
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 Glu Lys Phe Glu Asp Glu Asn Phe Ile Leu Lys His Thr Gly Pro Gly
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Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr
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Pro Glu Asn Tyr Val Tyr Gln Gly Arg Gln Glu Cys Tyr Ala Phe Asn
      35                      40                      45

```

```

Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
      50                      55                      60

```

```

Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
      65                      70                      75                      80

```

```

Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
      85                      90                      95

```

```

Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
      100                     105                     110

```

```

Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
      115                     120                     125

```

```

Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
      130                     135                     140

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His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
 145 150 155 160

Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg
 165 170 175

Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
 180 185 190

Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp
 195 200 205

Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser
 210 215 220

Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys
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Gly Val Gly Ile Phe Met His Arg Arg Ser Lys Lys Val Gln Arg Gly
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Ser Ala

<210> 100

<211> 5022

<212> DNA

<213> Homo sapiens

<400> 100

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63/147

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64/147

<210> 101

<211> 1356

<212> PRT

<213> Homo sapiens

<400> 101

Met Asp Leu Lys Glu Lys His Leu Gly Glu Pro Pro Ser Ala Leu Gly
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Leu Ser Thr Arg Lys Ala Leu Ser Val Leu Lys Glu Gln Leu Glu Ala
 20 25 30

Val Leu Glu Gly His Leu Arg Glu Arg Lys Lys Cys Leu Thr Trp Lys
 35 40 45

Glu Val Trp Arg Ser Ser Phe Leu His His Ser Asn Arg Cys Ser Cys
 50 55 60

Phe His Trp Pro Gly Ala Ser Leu Met Leu Leu Ala Val Leu Leu Leu
 65 70 75 80

Leu Gly Cys Cys Gly Gly Gln Pro Ala Gly Ser Arg Gly Val Gly Leu
 85 90 95

Val Asn Ala Ser Ala Leu Phe Leu Leu Leu Leu Asn Leu Val Leu
 100 105 110

Ile Gly Arg Gln Asp Arg Leu Lys Arg Arg Glu Val Glu Arg Arg Leu
 115 120 125

Arg Gly Ile Ile Asp Gln Ile Gln Asp Ala Leu Arg Asp Gly Arg Glu
 130 135 140

Ile Gln Trp Pro Ser Ala Met Tyr Pro Asp Leu His Met Pro Phe Ala
 145 150 155 160

Pro Ser Trp Ser Leu His Trp Ala Tyr Arg Asp Gly His Leu Val Asn
 165 170 175

Leu Pro Val Ser Leu Leu Val Glu Gly Asp Ile Ile Ala Leu Arg Pro
 180 185 190

Gly Gln Glu Ser Phe Ala Ser Leu Arg Gly Ile Lys Asp Asp Glu His
 195 200 205

Ile Val Leu Glu Pro Gly Asp Leu Phe Pro Pro Phe Ser Pro Pro Pro
 210 215 220

Ser Pro Arg Gly Glu Val Glu Arg Gly Pro Gln Ser Pro Gln Gln His
 225 230 235 240

Arg Leu Phe Arg Val Leu Glu Thr Pro Val Ile Asp Asn Ile Arg Trp
 245 250 255

Cys Leu Asp Met Ala Leu Ser Arg Pro Val Thr Ala Leu Asp Asn Glu
 260 265 270

65/147

Arg	Phe	Thr	Val	Gln	Ser	Val	Met	Leu	His	Tyr	Ala	Val	Pro	Val	Val
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Leu	Ala	Gly	Phe	Leu	Ile	Thr	Asn	Ala	Leu	Arg	Phe	Ile	Phe	Ser	Ala
	290					295					300				
Pro	Gly	Val	Thr	Ser	Trp	Gln	Tyr	Thr	Leu	Leu	Gln	Leu	Gln	Val	Asn
305					310					315					320
Gly	Val	Leu	Pro	Ile	Leu	Pro	Leu	Leu	Phe	Pro	Val	Leu	Trp	Val	Leu
				325					330					335	
Ala	Thr	Ala	Cys	Gly	Glu	Ala	Arg	Val	Leu	Ala	Gln	Met	Ser	Lys	Ala
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Ser	Pro	Ser	Ser	Leu	Leu	Ala	Lys	Phe	Ser	Glu	Asp	Thr	Leu	Ser	Ser
		355					360					365			
Tyr	Thr	Glu	Ala	Val	Ser	Ser	Gln	Glu	Met	Leu	Arg	Cys	Ile	Trp	Gly
	370					375					380				
His	Phe	Leu	Arg	Val	Leu	Gly	Gly	Thr	Ser	Pro	Thr	Leu	Ser	His	Ser
385					390					395					400
Ser	Ser	Leu	Leu	His	Ser	Leu	Gly	Ser	Val	Thr	Val	Leu	Cys	Cys	Val
				405					410					415	
Asp	Lys	Gln	Gly	Ile	Leu	Ser	Trp	Pro	Asn	Pro	Ser	Pro	Glu	Thr	Val
		420						425					430		
Leu	Phe	Phe	Ser	Gly	Lys	Val	Glu	Pro	Pro	His	Ser	Ser	His	Glu	Asp
		435					440					445			
Leu	Thr	Asp	Gly	Leu	Ser	Thr	Arg	Ser	Phe	Cys	His	Pro	Glu	Pro	His
	450					455					460				
Glu	Arg	Asp	Ala	Leu	Leu	Ala	Gly	Ser	Leu	Asn	Asn	Thr	Leu	His	Leu
465					470					475					480
Ser	Asn	Glu	Gln	Glu	Arg	Gly	Asp	Trp	Pro	Gly	Glu	Ala	Pro	Lys	Pro
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Pro	Glu	Pro	Tyr	Ser	His	His	Lys	Ala	His	Gly	Arg	Ser	Lys	His	Pro
			500					505					510		
Ser	Gly	Ser	Asn	Val	Ser	Phe	Ser	Arg	Asp	Thr	Glu	Gly	Gly	Glu	Glu
		515					520					525			
Glu	Pro	Ser	Lys	Thr	Gln	Pro	Gly	Met	Glu	Ser	Asp	Pro	Tyr	Glu	Ala
	530					535					540				
Glu	Asp	Phe	Val	Cys	Asp	Tyr	His	Leu	Glu	Met	Leu	Ser	Leu	Ser	Gln
545					550					555					560
Asp	Gln	Gln	Asn	Pro	Ser	Cys	Ile	Gln	Phe	Asp	Asp	Ser	Asn	Trp	Gln
				565					570					575	

66/147

Leu His Leu Thr Ser Leu Lys Pro Leu Gly Leu Asn Val Leu Leu Asn
 580 585 590
 Leu Cys Asp Ala Ser Val Thr Glu Arg Leu Cys Arg Phe Ser Asp His
 595 600 605
 Leu Cys Asn Ile Ala Leu Gln Glu Ser His Ser Ala Val Leu Pro Val
 610 615 620
 His Val Pro Trp Gly Leu Cys Glu Leu Ala Arg Leu Ile Gly Phe Thr
 625 630 635 640
 Pro Gly Ala Lys Glu Leu Phe Lys Gln Glu Asn His Leu Ala Leu Tyr
 645 650 655
 Arg Leu Pro Ser Ala Glu Thr Met Lys Glu Thr Ser Leu Gly Arg Leu
 660 665 670
 Ser Cys Val Thr Lys Arg Arg Pro Pro Leu Ser His Met Ile Ser Leu
 675 680 685
 Phe Ile Lys Asp Thr Thr Thr Ser Thr Glu Gln Met Leu Ser His Gly
 690 695 700
 Thr Ala Asp Val Val Leu Glu Ala Cys Thr Asp Phe Trp Asp Gly Ala
 705 710 715 720
 Asp Ile Tyr Pro Leu Ser Gly Ser Asp Arg Lys Lys Val Leu Asp Phe
 725 730 735
 Tyr Gln Arg Ala Cys Leu Ser Gly Tyr Cys Ser Ala Phe Ala Tyr Lys
 740 745 750
 Pro Met Asn Cys Ala Leu Ser Ser Gln Leu Asn Gly Lys Cys Ile Glu
 755 760 765
 Leu Val Gln Val Pro Gly Gln Ser Ser Ile Phe Thr Met Cys Glu Leu
 770 775 780
 Pro Ser Thr Ile Pro Ile Lys Gln Asn Ala Arg Arg Ser Ser Trp Ser
 785 790 795 800
 Ser Asp Glu Gly Ile Gly Glu Val Leu Glu Lys Glu Asp Cys Met Gln
 805 810 815
 Ala Leu Ser Gly Gln Ile Phe Met Gly Met Val Ser Ser Gln Tyr Gln
 820 825 830
 Ala Arg Leu Asp Ile Val Arg Leu Ile Asp Gly Leu Val Asn Ala Cys
 835 840 845
 Ile Arg Phe Val Tyr Phe Ser Leu Glu Asp Glu Leu Lys Ser Lys Val
 850 855 860
 Phe Ala Glu Lys Met Gly Leu Glu Thr Gly Trp Asn Cys His Ile Ser
 865 870 875 880

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Leu Thr Pro Asn Gly Asp Met Pro Gly Ser Glu Ile Pro Pro Ser Ser
 885 890 895
 Pro Ser His Ala Gly Ser Leu His Asp Asp Leu Asn Gln Val Ser Arg
 900 905 910
 Asp Asp Ala Glu Gly Leu Leu Leu Met Glu Glu Glu Gly His Ser Asp
 915 920 925
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 Asp Ser Asn Arg Ala Lys Leu Pro Arg Gly Ile His Gln Val Arg Pro
 945 950 955 960
 His Leu Gln Asn Ile Asp Asn Val Pro Leu Leu Val Pro Leu Phe Thr
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 Asp Cys Thr Pro Glu Thr Met Cys Glu Met Ile Lys Ile Met Gln Glu
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 Tyr Gly Glu Val Thr Cys Cys Leu Gly Ser Ser Ala Asn Leu Arg Asn
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 Ser Cys Leu Phe Leu Gln Ser Asp Ile Ser Ile Ala Leu Asp Pro Leu
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 Val Ile Gln Phe Leu Ser Cys Leu Val Gln Leu Pro Pro Leu Leu Ser
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 Thr Thr Asp Ile Leu Trp Leu Ser Cys Phe Cys Tyr Pro Leu Leu Ser
 1125 1130 1135
 Ile Ser Leu Leu Gly Lys Pro Pro His Ser Ser Ile Met Ser Met Ala
 1140 1145 1150
 Thr Gly Lys Asn Leu Gln Ser Ile Pro Lys Lys Thr Gln His Tyr Phe
 1155 1160 1165
 Leu Leu Cys Phe Leu Leu Lys Phe Ser Leu Thr Ile Ser Ser Cys Leu
 1170 1175 1180

68/147

Ile Cys Phe Gly Phe Thr Leu Gln Ser Phe Cys Asp Ser Ser Arg Asp
 1185 1190 1195 1200

Arg Asn Leu Thr Asn Cys Ser Ser Val Met Leu Pro Ser Asn Asp Asp
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Arg Ala Pro Ala Trp Phe Glu Asp Phe Ala Asn Gly Leu Leu Ser Ala
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Gln Lys Leu Thr Ala Ala Leu Ile Val Leu His Thr Val Phe Ile Ser
 1235 1240 1245

Ile Thr His Val His Arg Thr Lys Pro Leu Trp Arg Lys Ser Pro Leu
 1250 1255 1260

Thr Asn Leu Trp Trp Ala Val Thr Val Pro Val Val Leu Leu Gly Gln
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Val Val Gln Thr Ala Val Asp Leu Gln Leu Trp Thr His Arg Asp Ser
 1285 1290 1295

His Val His Phe Gly Leu Glu Asp Val Pro Leu Leu Thr Trp Leu Leu
 1300 1305 1310

Gly Cys Leu Ser Leu Val Leu Val Val Val Thr Asn Glu Ile Val Lys
 1315 1320 1325

Leu His Glu Ile Arg Val Arg Val Arg Tyr Gln Lys Arg Gln Lys Leu
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Gln Phe Glu Thr Lys Leu Gly Met Asn Ser Pro Phe
 1345 1350 1355

<210> 102

<211> 2030

<212> DNA

<213> Homo sapiens

<400> 102

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69/147

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<210> 103

<211> 318

<212> PRT

<213> Homo sapiens

<400> 103

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Met Ser Lys Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp
 1          5          10          15

Ser Arg Thr Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala
      20          25          30

Asp Asp Leu Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val
      35          40          45

Val Glu Lys Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys
      50          55          60

Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met
      65          70          75          80

Asp Leu Asp Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr
      85          90          95

Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu
      100          105          110

Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys
      115          120          125

Asn Met Thr Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile
      130          135          140

Val Arg Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile His Arg
      145          150          155          160

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys Glu Gly His Val Lys
      165          170          175

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Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys
 180 185 190

Thr Met Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn
 195 200 205

Pro Glu Leu Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser
 210 215 220

Leu Gly Ile Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu
 225 230 235 240

Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro
 245 250 255

Ser Pro Gln Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe
 260 265 270

Thr Ala Gln Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu
 275 280 285

Glu Leu Met Glu His Pro Phe Phe Thr Leu His Lys Thr Lys Lys Thr
 290 295 300

Asp Ile Ala Ala Phe Val Lys Lys Ile Leu Gly Glu Asp Ser
 305 310 315

<210> 104

<211> 1648

<212> DNA

<213> Homo sapiens

<400> 104

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gacttgacg tcggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg 180
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gaaccctaca acgccacgct gtccatccac cagctggtgg aaaacacgga tgaaacctac 600
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gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgta cgaagacgac 1320
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71/147

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accctgcttt ccccatcgcc ctagggtccc cttgccgccc tccctgcagta tttatggcct 1500
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ggcctgacgt tttacgggtt tggttttttac tggtttgtgt ttatatatttc ggggatactt 1620
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<210> 105

<211> 450

<212> PRT

<213> Homo sapiens

<400> 105

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Met Arg Glu Ile Val His Ile Gln Ala Gly Gln Cys Gly Asn Gln Ile
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Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
      20          25          30

Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
      35          40          45

Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
      50          55          60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
      65          70          75          80

Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
      85          90          95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
      100          105          110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
      115          120          125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
      130          135          140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
      145          150          155          160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
      165          170          175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
      180          185          190

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
      195          200          205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
      210          215          220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
      225          230          235          240

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Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
 245 250 255
 Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
 260 265 270
 Leu Thr Arg Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
 275 280 285
 Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
 290 295 300
 Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Arg
 305 310 315 320
 Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Ser Lys
 325 330 335
 Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
 340 345 350
 Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ser Thr Phe Ile
 355 360 365
 Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
 370 375 380
 Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
 385 390 395 400
 Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
 405 410 415
 Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
 420 425 430
 Glu Gly Glu Met Tyr Glu Asp Asp Glu Glu Glu Ser Glu Ala Gln Gly
 435 440 445
 Pro Lys
 450

<210> 106

<211> 1633

<212> DNA

<213> Homo sapiens

<400> 106

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 catttaaaag gtagaacagg atcgacaaac aaggatttat gtcaggatct ctcagcctct 180
 gtgttaccga gggcattttct aacagtcttc ttactacggc ctccgccgac cgcgcgctcg 240
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 ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg agctggtgtc 420
 actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa 480
 agatgccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt 540

73/147

```

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aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga 720
gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaaat atgaagaggt 780
ggcccgtaa gctggtcatca ttgagagcga cctggaacgt gcagaggagc gggctgagct 840
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caaagtgcca atgatagagt caacaaggaa ggtaaatgtt ggaaacacaa tcaggtgtgg 1500
attggtgcta ctttgaacaa aagggtcccc tgtggtcttt tgttcaacat tgtacaatgt 1560
agaactctgt ccaacactaa tttattttgt cttgagtttt actacaagat gagactatgt 1620
atcccgcattg cct                                     1633

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<210> 107

<211> 284

<212> PRT

<213> Homo sapiens

<400> 107

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Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
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Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
      20              25              30
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
      35              40              45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
      50              55              60
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
      65              70              75              80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
      85              90              95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
      100             105             110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
      115             120             125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
      130             135             140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
      145             150             155             160

```

Lys	Tyr	Glu	Glu	Val 165	Ala	Arg	Lys	Leu	Val 170	Ile	Ile	Glu	Ser	Asp 175	Leu
Glu	Arg	Ala	Glu 180	Glu	Arg	Ala	Glu	Leu 185	Ser	Glu	Gly	Gln	Val 190	Arg	Gln
Leu	Glu	Glu 195	Gln	Leu	Arg	Ile	Met 200	Asp	Gln	Thr	Leu	Lys 205	Ala	Leu	Met
Ala	Ala 210	Glu	Asp	Lys	Tyr	Ser 215	Gln	Lys	Glu	Asp	Arg 220	Tyr	Glu	Glu	Glu
Ile 225	Lys	Val	Leu	Ser 230	Asp	Lys	Leu	Lys	Glu 235	Ala	Glu	Thr	Arg	Ala	Glu 240
Phe	Ala	Glu	Arg	Ser 245	Val	Thr	Lys	Leu	Glu 250	Lys	Ser	Ile	Asp	Asp 255	Leu
Glu	Glu	Lys	Val 260	Ala	His	Ala	Lys	Glu 265	Glu	Asn	Leu	Ser	Met 270	His	Gln
Met	Leu	Asp 275	Gln	Thr	Leu	Leu	Glu 280	Leu	Asn	Asn	Met				

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<222> (71)..(71)  
<223> n is a, c, g, or t
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<400> 108						
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caaaagctgg	agctcgcg	cctgcaggtc	gacactagtg	gatccaaaga	attcggcacg	180
aggcgacggg	cggagcggag	cgcggcgcgc	cggggccgcc	gccgggggga	tcggctgcct	240
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cataggaggc	ggccatggcg	acccccggca	acctagggtc	ctccgtcctg	gcgagcaaga	360
ccaagaccaa	gaagaagcac	ttcgtagcgc	agaaagtga	gctgtttcgg	gccagcgacc	420
cgctgctcag	cgtcctcatg	tggggggtaa	accactcgat	caatgaactg	agccatgttc	480
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tgaccaggag	cgcacccctc	cccaacgact	cccaggcccc	cagtggagct	cgttttcaca	720
cttcctacga	caaaagatac	atgatcaaga	ctattaccag	tgaagacgtg	gccgaaatgc	780
acaacatcct	gaagaataac	caccagtaca	tagtgaattg	tcatgggatc	acccttcttc	840
cccacttggt	gggcatgtac	cggcttaatg	ttgatggagt	tgaatatatat	gtgatagtta	900
caagaaatgt	attcagccac	cgtttgtctg	tgtataggaa	atacgactta	aagggtccta	960
cagtggctag	agaagctagt	gacaaagaaa	aggccaaaga	actgccaaact	ctgaaagata	1020

75/147

```

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<210> 109

<211> 406

<212> PRT

<213> Homo sapiens

<400> 109

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Met Ala Thr Pro Gly Asn Leu Gly Ser Ser Val Leu Ala Ser Lys Thr
  1              5              10              15

Lys Thr Lys Lys Lys His Phe Val Ala Gln Lys Val Lys Leu Phe Arg
          20              25              30

Ala Ser Asp Pro Leu Leu Ser Val Leu Met Trp Gly Val Asn His Ser
  35              40              45

Ile Asn Glu Leu Ser His Val Gln Ile Pro Val Met Leu Met Pro Asp
  50              55              60

Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp Asn His Leu Phe Asn
  65              70              75              80

Lys Glu Asn Met Pro Ser His Phe Lys Phe Lys Glu Tyr Cys Pro Met
          85              90              95

Val Phe Arg Asn Cys Gly Lys Arg Phe Gly Ile Asp Val Gln Asp Phe
          100              105              110

Gln Asn Ser Leu Thr Arg Ser Ala Pro Leu Pro Asn Asp Ser Gln Ala
          115              120              125

Arg Ser Gly Ala Arg Phe His Thr Ser Tyr Asp Lys Arg Tyr Met Ile
          130              135              140

Lys Thr Ile Thr Ser Glu Asp Val Ala Glu Met His Asn Ile Leu Lys
          145              150              155              160

Lys Tyr His Gln Tyr Ile Val Glu Cys His Gly Ile Thr Leu Leu Pro
          165              170              175

His Leu Leu Gly Met Tyr Arg Leu Asn Val Asp Gly Val Glu Ile Tyr
          180              185              190

```

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Val Ile Val Thr Arg Asn Val Phe Ser His Arg Leu Ser Val Tyr Arg
 195 200 205

Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg Glu Ala Ser Asp Lys
 210 215 220

Glu Lys Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn
 225 230 235 240

Glu Gly Gln Lys Ile Tyr Ile Asp Asp Asn Ser Lys Lys Val Phe Leu
 245 250 255

Glu Lys Leu Lys Lys Asp Val Glu Phe Leu Ala Gln Leu Lys Leu Met
 260 265 270

Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val Glu Arg Ala Glu Gln
 275 280 285

Glu Glu Val Glu Cys Glu Glu Asn Asp Gly Glu Glu Glu Gly Glu Ser
 290 295 300

Asp Gly Thr His Pro Val Gly Thr Pro Pro Asp Ser Pro Gly Asn Thr
 305 310 315 320

Leu Asn Ser Ser Pro Pro Leu Ala Pro Gly Glu Phe Glu Pro Asn Ile
 325 330 335

Asp Val Tyr Gly Ile Lys Cys His Glu Asn Ser Pro Arg Lys Glu Val
 340 345 350

Tyr Phe Met Ala Ile Ile Asp Ile Leu Thr His Tyr Asp Ala Lys Lys
 355 360 365

Lys Ala Ala His Ala Ala Lys Thr Val Lys His Gly Ala Gly Ala Glu
 370 375 380

Ile Ser Thr Val Asn Pro Glu Gln Tyr Ser Lys Arg Phe Leu Asp Phe
 385 390 395 400

Ile Gly His Ile Leu Thr
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<210> 110

<211> 2572

<212> DNA

<213> Homo sapiens

<400> 110

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gaagtgattt ttttgccctc ctcagcttta ttctctttt cctctgaact gtagagtcta 360
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77/147

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 <211> 197
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Thr Ala Asp Gln Ile Glu Glu Phe Lys Glu Ala Phe Ser Leu Phe Asp
 50 55 60
 Arg Thr Pro Thr Gly Glu Met Lys Ile Thr Tyr Gly Gln Cys Gly Asp
 65 70 75 80

<400> 113
Met Lys Val Glu Val Leu Pro Ala Leu Thr Asp Asn Tyr Met Tyr Leu
1 5 10 15

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Val Ile Asp Asp Glu Thr Lys Glu Ala Ala Ile Val Asp Pro Val Gln
 20 25 30
 Pro Gln Lys Val Val Asp Ala Ala Arg Lys His Gly Val Lys Leu Thr
 35 40 45
 Thr Val Leu Thr Thr His His His Trp Asp His Ala Gly Gly Asn Glu
 50 55 60
 Lys Leu Val Lys Leu Glu Ser Gly Leu Lys Val Tyr Gly Gly Asp Asp
 65 70 75 80
 Arg Ile Gly Ala Leu Thr His Lys Ile Thr His Leu Ser Thr Leu Gln
 85 90 95
 Val Gly Ser Leu Asn Val Lys Cys Leu Ala Thr Pro Cys His Thr Ser
 100 105 110
 Gly His Ile Cys Tyr Phe Val Ser Lys Pro Gly Gly Ser Glu Pro Pro
 115 120 125
 Ala Val Phe Thr Gly Asp Thr Leu Phe Val Ala Gly Cys Gly Lys Phe
 130 135 140
 Tyr Glu Gly Thr Ala Asp Glu Met Cys Lys Ala Leu Leu Glu Val Leu
 145 150 155 160
 Gly Arg Leu Pro Pro Asp Thr Arg Val Tyr Cys Gly His Glu Tyr Thr
 165 170 175
 Ile Asn Asn Leu Lys Phe Ala Arg His Val Glu Pro Gly Asn Ala Ala
 180 185 190
 Ile Arg Glu Lys Leu Ala Trp Ala Lys Glu Lys Tyr Ser Ile Gly Glu
 195 200 205
 Pro Thr Val Pro Ser Thr Leu Ala Glu Glu Phe Thr Tyr Asn Pro Phe
 210 215 220
 Met Arg Val Arg Glu Lys Thr Val Gln Gln His Ala Gly Glu Thr Asp
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 245 250 255
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<212> DNA

<213> Homo sapiens

<400> 114

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80/147

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<213> Homo sapiens

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Val Arg Pro Ser Ala Gly Asn Val Ser Thr His Pro Ser Leu Ser Gln
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Asp Ser Pro Ser Lys Ser Ser Ala Glu Ala Gln Thr Pro Glu Asp Thr
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 Gly Ser Glu Ala Gln Thr Thr Lys Asp Ser Thr Ser Lys Ser His Pro
 115 120 125
 Glu Leu Gln Thr Pro Lys Asp Ser Thr Gly Lys Ser Gly Ala Glu Ala
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 Gln Thr Pro Glu Asp Ser Pro Asn Arg Ser Gly Ala Glu Pro Lys Thr
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 Gln Lys Asp Ser Pro Ser Lys Ser Gly Ser Glu Ala Gln Thr Thr Lys
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 Asp Val Pro Asn Lys Ser Gly Ala Asp Gly Gln Thr Pro Lys Asp Gly
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 Ser Ser Lys Ser Gly Ala Glu Asp Gln Thr Pro Lys Asp Val Pro Asn
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 Lys Ser Gly Ala Glu Lys Gln Thr Pro Lys Asp Gly Ser Asn Lys Ser
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 Gly Ala Glu Glu Gln Gly Pro Ile Asp Gly Pro Ser Lys Ser Gly Ala
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 245 250 255
 Pro Ser Arg Lys Asp His Ser Lys Pro Ile Ser Asn Pro Ser Asp Asn
 260 265 270
 Lys Glu Leu Pro Lys Ala Asp Thr Asn Gln Leu Ala Asp Lys Gly Lys
 275 280 285
 Leu Ser Pro His Ala Phe Lys Thr Glu Ser Gly Glu Glu Thr Asp Leu
 290 295 300
 Ile Ser Pro Pro Gln Glu Glu Val Lys Ser Ser Glu Pro Thr Glu Asp
 305 310 315 320
 Val Gly Pro Lys Glu Ala Glu Asp Asp Asp Thr Gly Pro Glu Glu Gly
 325 330 335
 Ser Pro Pro Lys Glu Glu Lys Glu Lys Met Ser Gly Ser Ala Ser Ser
 340 345 350
 Glu Asn Arg Glu Gly Thr Leu Ser Asp Ser Thr Gly Ser Glu Lys Asp
 355 360 365
 Asp Leu Tyr Pro Asn Gly Ser Gly Asn Gly Ser Ala Glu Ser Ser His
 370 375 380

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Phe Phe Ala Tyr Leu Val Thr Ala Ala Ile Leu Val Ala Val Leu Tyr
 385 390 395 400
 Ile Ala His His Asn Lys Arg Lys Ile Ile Ala Phe Val Leu Glu Gly
 405 410 415
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 Leu Asp Gln Lys Ile Phe Ser Pro Pro Ser Pro Asn Arg Met Val Tyr
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 Ser Ser Gly Lys Arg
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 gggtagaggct tcccgcctgg cgcattacaa caagcgctcg accatcaoct ccagggagat 300
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 caccaaggcc gtcaccaagt acaccagcgc taagtaaaact tgccaaggag ggactttctc 420
 tggaaatttc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcggt 480
 tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt 540
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 Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn
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 Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg
 65 70 75 80

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Leu Ala His Tyr Asn Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln
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Thr Ala Val Arg Leu Leu Leu Pro Gly Glu Leu Ala Lys His Ala Val
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Ser Glu Gly Thr Lys Ala Val Thr Lys Tyr Thr Ser Ala Lys
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gacccccagc	tctgaagaga	tcagccctac	taagtcttct	ggattgtacc	gcaactggcg	360
gccctcacct	ccccatgaca	tcttccatga	gcctcctgat	gtagtgtctg	atgatgagaa	420
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Pro Pro His Asp Ile Leu His Glu Pro Pro Asp Val Val Ser Asp Asp
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Glu Lys Asp His Gly Lys Lys Lys Gly Lys Phe Lys Lys Lys Glu Lys
 65                               70                               75                               80

Arg Thr Glu Gly Tyr Ala Ala Phe Gln Glu Asp Ser Ser Gly Asp Glu
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Ala Glu Ser Pro Ser Lys Met Lys Arg Ser Lys Gly Ile His Val Phe
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Lys Lys Pro Ser Phe Ser Lys Lys Lys Glu Lys Asp Phe Lys Ile Lys
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Glu Lys Pro Lys Glu Glu Lys His Lys Glu Glu Lys His Lys Glu Glu
 130                               135                               140

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 Pro Leu Ala Asp Ala Val Glu Arg Thr Met Met Tyr Asp Gly Ile Arg
 195 200 205
 Leu Pro Ala Val Phe Arg Glu Cys Ile Asp Tyr Val Glu Lys Tyr Gly
 210 215 220
 Met Lys Cys Glu Gly Ile Tyr Arg Val Ser Gly Ile Lys Ser Lys Val
 225 230 235 240
 Asp Glu Leu Lys Ala Ala Tyr Asp Arg Glu Glu Ser Thr Asn Leu Glu
 245 250 255
 Asp Tyr Glu Pro Asn Thr Val Ala Ser Leu Leu Lys Gln Tyr Leu Arg
 260 265 270
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 275 280 285
 Glu Ala Cys Gly Arg Thr Thr Glu Thr Glu Lys Val Gln Glu Phe Gln
 290 295 300
 Arg Leu Leu Lys Glu Leu Pro Glu Cys Asn Tyr Leu Leu Ile Ser Trp
 305 310 315 320
 Leu Ile Val His Met Asp His Val Ile Ala Lys Glu Leu Glu Thr Lys
 325 330 335
 Met Asn Ile Gln Asn Ile Ser Ile Val Leu Ser Pro Thr Val Gln Ile
 340 345 350
 Ser Asn Arg Val Leu Tyr Val Phe Phe Thr His Val Gln Glu Leu Phe
 355 360 365
 Gly Asn Val Val Leu Lys Gln Val Met Lys Pro Leu Arg Trp Ser Asn
 370 375 380
 Met Ala Thr Met Pro Thr Leu Pro Glu Thr Gln Ala Gly Ile Lys Glu
 385 390 395 400
 Glu Ile Arg Arg Gln Glu Phe Leu Leu Asn Cys Leu His Arg Asp Leu
 405 410 415
 Gln Gly Gly Ile Lys Asp Leu Ser Lys Glu Glu Arg Leu Trp Glu Val
 420 425 430
 Gln Arg Ile Leu Thr Ala Leu Lys Arg Lys Leu Arg Glu Ala Lys Arg
 435 440 445

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Gln Glu Cys Glu Thr Lys Ile Ala Gln Glu Ile Ala Ser Leu Ser Lys
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 Glu Asp Val Ser Lys Glu Glu Met Asn Glu Asn Glu Glu Val Ile Asn
 465 470 475 480
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 Leu Ala Met Glu Gln Phe Leu Arg Arg Gln Ile Ala Ser Glu Lys Glu
 500 505 510
 Glu Ile Glu Arg Leu Arg Ala Glu Ile Ala Glu Ile Gln Ser Arg Gln
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 Gln His Gly Arg Ser Glu Thr Glu Glu Tyr Ser Ser Glu Ser Glu Ser
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 Glu Ser Glu Asp Glu Glu Glu Leu Gln Ile Ile Leu Glu Asp Leu Gln
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 Arg Gln Asn Glu Glu Leu Glu Ile Lys Asn Asn His Leu Asn Gln Ala
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 Ile His Glu Glu Arg Glu Ala Ile Ile Glu Leu Arg Val Gln Leu Arg
 580 585 590
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 cactgatgag ntctgggggn tctgcacaca cccctcccag aaccgnttcc tcacctgcgg 180
 ccacgaccgg nagttctgcc tgtgggatgg ggagagccat gcactggcct ggagcatcga 240
 cctcaaggag actggtctct gtgctgactt ccacccgagt ggggcagttg tggccgnagg 300
 actgaacacg gggaggtggt tgggttttgn cacagagacc agagagatcg tgtctgatgt 360
 cattgatggc aatnagcagc tctcagtggc ccggtacagn ccagatgggt tggtcctggc 420
 ccaattggtt ccccatnaca acntnatntt caatcttttn gnggtttcca ggggatgggt 480
 cccaattcca gncnttttgg ggccntttgt ntttgggtca acncccagnt tcaaccactc 540
 aatnttggag taggttcaan nnttngnntt accagttggn nttntccaan nnnnnnnnnn 600
 nntntnnntt nnttnttctt ttncntnann cnnnnnnnnn nncnnntctn cntnttnntc 660
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<210> 121
 <211> 1211
 <212> DNA
 <213> Homo sapiens

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 gactacactt cccgtcggcc cgctgctct cccgatgccg ccttggcgcg agacgttggc 240
 aagcagagt tctccaagat ggccgcttgg ggaaggaggc gtcttgccc gggcagcagt 300
 ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtgcatgag 360

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gccagtaga agtacattgt gattgagccc actcgcatg gcgacgagac agcccgtctg 480
atcacctgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctcttc 540
accccgcttg cgctgccctt agattattcc cactacattt ccctgccgcg tgggtgtgctg 600
agcctggcct gctgcaccct ctatgggatc tcctggcagt ttgacccttg ctgcaagtac 660
caagtggagt acgacgccta taaactgtcg cgctgcctc tgcacacact cacctcctcc 720
accccggtgg tgctggtccg gaaggacgac ctgcacagaa agagactgca caacacgata 780
gcactggccg ccctggtgta ctgtgtaaag aagatttacg aactctatgc cgtatgattt 840
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tcgccacact ctgtgaggca gcagagcctg ggcaggtgtt tggcttagta tttgttattt 960
ttaaaaaata acagatcacg ggtgtaccca ggtttttca gctcattaca ctaagatgtg 1020
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<210> 122

<211> 192

<212> PRT

<213> Homo sapiens

<400> 122

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Met Ala Ala Trp Gly Arg Arg Arg Leu Gly Pro Gly Ser Ser Gly Gly
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Ser Ala Arg Glu Arg Val Ser Leu Ser Ala Thr Asp Cys Tyr Ile Val
          20             25             30

His Glu Ile Tyr Asn Gly Glu Asn Ala Gln Asp Gln Phe Glu Tyr Glu
      35             40             45

Leu Glu Gln Ala Leu Glu Ala Gln Tyr Lys Tyr Ile Val Ile Glu Pro
      50             55             60

Thr Arg Ile Gly Asp Glu Thr Ala Arg Trp Ile Thr Val Gly Asn Cys
      65             70             75             80

Leu His Lys Thr Ala Val Leu Ala Gly Thr Ala Cys Leu Phe Thr Pro
          85             90             95

Leu Ala Leu Pro Leu Asp Tyr Ser His Tyr Ile Ser Leu Pro Ala Gly
      100             105             110

Val Leu Ser Leu Ala Cys Cys Thr Leu Tyr Gly Ile Ser Trp Gln Phe
      115             120             125

Asp Pro Cys Cys Lys Tyr Gln Val Glu Tyr Asp Ala Tyr Lys Leu Ser
      130             135             140

Arg Leu Pro Leu His Thr Leu Thr Ser Ser Thr Pro Val Val Leu Val
      145             150             155             160

Arg Lys Asp Asp Leu His Arg Lys Arg Leu His Asn Thr Ile Ala Leu
          165             170             175

Ala Ala Leu Val Tyr Cys Val Lys Lys Ile Tyr Glu Leu Tyr Ala Val
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 <211> 1568
 <212> DNA
 <213> Homo sapiens

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 agcgagcccc ggccgcccgc accaccagcc gcgctaaccg ccgaccaacc gccaccgagg 180
 cgcttgagcg agagcagagg aggaggagg atgagtgagg cgggcgaggc caccaccacc 240
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 tatctgcgca gtgtaggaga tggagaaact gtagagtttg atgtggttga aggagagaag 660
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 tctttaagaa acaactacaa aaagaaaatg tcaacaaatt tttccagcaa gctgagaacc 1560
 tggaaattc 1568

<210> 124
 <211> 412
 <212> PRT
 <213> Homo sapiens

<400> 124
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 20 25 30
 Glu Ile Arg Pro Gly Leu Pro Glu Ser Glu Pro Arg Pro Arg Pro
 35 40 45
 Pro Ala Ala Leu Thr Ala Asp Gln Pro Pro Pro Arg Arg Leu Ser Glu
 50 55 60

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Ser Arg Gly Gly Gly Gly Met Ser Glu Ala Gly Glu Ala Thr Thr Thr
 65 70 75 80
 Thr Thr Thr Thr Leu Pro Gln Ala Pro Thr Glu Ala Ala Ala Ala Ala
 85 90 95
 Pro Gln Asp Pro Ala Pro Lys Ser Pro Val Gly Ser Gly Ala Pro Gln
 100 105 110
 Ala Ala Ala Pro Ala Pro Ala Ala His Val Ala Gly Asn Pro Gly Gly
 115 120 125
 Asp Ala Ala Pro Ala Ala Thr Gly Thr Ala Ala Ala Ala Ser Leu Ala
 130 135 140
 Ala Ala Ala Gly Ser Glu Asp Ala Glu Lys Lys Val Leu Ala Thr Lys
 145 150 155 160
 Val Leu Gly Thr Val Lys Trp Phe Asn Val Arg Asn Gly Tyr Gly Phe
 165 170 175
 Ile Asn Arg Asn Asp Thr Lys Glu Asp Val Phe Val His Gln Thr Ala
 180 185 190
 Ile Lys Lys Asn Asn Pro Arg Lys Tyr Leu Arg Ser Val Gly Asp Gly
 195 200 205
 Glu Thr Val Glu Phe Asp Val Val Glu Gly Glu Lys Gly Ala Glu Ala
 210 215 220
 Ala Asn Val Thr Gly Pro Asp Gly Val Pro Val Glu Gly Ser Arg Tyr
 225 230 235 240
 Ala Ala Asp Arg Arg Arg Tyr Arg Arg Gly Tyr Tyr Gly Arg Arg Arg
 245 250 255
 Gly Pro Pro Arg Asn Tyr Ala Gly Glu Glu Glu Glu Gly Ser Gly
 260 265 270
 Ser Ser Glu Gly Phe Asp Pro Pro Ala Thr Asp Arg Gln Phe Ser Gly
 275 280 285
 Ala Arg Asn Gln Leu Arg Arg Pro Gln Tyr Arg Pro Gln Tyr Arg Gln
 290 295 300
 Arg Arg Phe Pro Pro Tyr His Val Gly Gln Thr Phe Asp Arg Arg Ser
 305 310 315 320
 Arg Val Leu Pro His Pro Asn Arg Ile Gln Ala Gly Glu Ile Gly Glu
 325 330 335
 Met Lys Asp Gly Val Pro Glu Gly Ala Gln Leu Gln Gly Pro Val His
 340 345 350
 Arg Asn Pro Thr Tyr Arg Pro Arg Tyr Arg Ser Arg Gly Pro Pro Arg
 355 360 365

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Pro Arg Pro Ala Pro Ala Val Gly Glu Ala Glu Asp Lys Glu Asn Gln
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Gln Ala Thr Ser Gly Pro Asn Gln Pro Ser Val Arg Arg Gly Tyr Arg
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Arg Pro Tyr Asn Tyr Arg Arg Arg Pro Pro Ser Ser
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<210> 125

<211> 2963

<212> DNA

<213> Homo sapiens

<400> 125

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<211> 930

<212> PRT

<213> Homo sapiens

<400> 126

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      20              25              30

Ile Asp Ile Tyr Ser Leu Thr Val Asp Ser Arg Val Ser Ser Arg Phe
      35              40              45

Ala His Thr Val Val Thr Ser Arg Val Val Asn Arg Ala Asn Thr Val
      50              55              60

Gln Glu Ala Thr Phe Gln Met Glu Leu Pro Lys Lys Ala Phe Ile Thr
      65              70              75              80

Asn Phe Ser Met Asn Ile Asp Gly Met Thr Tyr Pro Gly Ile Ile Lys
      85              90              95

Glu Lys Ala Glu Ala Gln Ala Gln Tyr Ser Ala Ala Val Ala Lys Gly
      100              105              110

Lys Asn Ala Gly Leu Val Lys Ala Thr Gly Arg Asn Met Glu Gln Phe
      115              120              125

Gln Val Ser Val Ser Val Ala Pro Asn Ala Lys Ile Thr Phe Glu Leu
      130              135              140

Val Tyr Glu Glu Leu Leu Lys Arg Arg Leu Gly Val Tyr Glu Leu Leu
      145              150              155              160

Leu Lys Val Arg Pro Gln Gln Leu Val Lys His Leu Gln Met Asp Ile
      165              170              175

His Ile Phe Glu Pro Gln Gly Ile Ser Phe Leu Glu Thr Glu Ser Thr
      180              185              190

Phe Met Thr Asn Gln Leu Val Asp Ala Leu Thr Thr Trp Gln Asn Lys
      195              200              205

Thr Lys Ala His Ile Arg Phe Lys Pro Thr Leu Ser Gln Gln Gln Lys
      210              215              220

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Ser	Pro	Glu	Gln	Gln	Glu	Thr	Val	Leu	Asp	Gly	Asn	Leu	Ile	Ile	Arg	225	230	235	240
Tyr	Asp	Val	Asp	Arg	Ala	Ile	Ser	Gly	Gly	Ser	Ile	Gln	Ile	Glu	Asn	245	250	255	
Gly	Tyr	Phe	Val	His	Tyr	Phe	Ala	Pro	Glu	Gly	Leu	Thr	Thr	Met	Pro	260	265	270	
Lys	Asn	Val	Val	Phe	Val	Ile	Asp	Lys	Ser	Gly	Ser	Met	Ser	Gly	Arg	275	280	285	
Lys	Ile	Gln	Gln	Thr	Arg	Glu	Ala	Leu	Ile	Lys	Ile	Leu	Asp	Asp	Leu	290	295	300	
Ser	Pro	Arg	Asp	Gln	Phe	Asn	Leu	Ile	Val	Phe	Ser	Thr	Glu	Ala	Thr	305	310	315	320
Gln	Trp	Arg	Pro	Ser	Leu	Val	Pro	Ala	Ser	Ala	Glu	Asn	Val	Asn	Lys	325	330	335	
Ala	Arg	Ser	Phe	Ala	Ala	Gly	Ile	Gln	Ala	Leu	Gly	Gly	Thr	Asn	Ile	340	345	350	
Asn	Asp	Ala	Met	Leu	Met	Ala	Val	Gln	Leu	Leu	Asp	Ser	Ser	Asn	Gln	355	360	365	
Glu	Glu	Arg	Leu	Pro	Glu	Gly	Ser	Val	Ser	Leu	Ile	Ile	Leu	Leu	Thr	370	375	380	
Asp	Gly	Asp	Pro	Thr	Val	Gly	Glu	Thr	Asn	Pro	Arg	Ser	Ile	Gln	Asn	385	390	395	400
Asn	Val	Arg	Glu	Ala	Val	Ser	Gly	Arg	Tyr	Ser	Leu	Phe	Cys	Leu	Gly	405	410	415	
Phe	Gly	Phe	Asp	Val	Ser	Tyr	Ala	Phe	Leu	Glu	Lys	Leu	Ala	Leu	Asp	420	425	430	
Asn	Gly	Gly	Leu	Ala	Arg	Arg	Ile	His	Glu	Asp	Ser	Asp	Ser	Ala	Leu	435	440	445	
Gln	Leu	Gln	Asp	Phe	Tyr	Gln	Glu	Val	Ala	Asn	Pro	Leu	Leu	Thr	Ala	450	455	460	
Val	Thr	Phe	Glu	Tyr	Pro	Ser	Asn	Ala	Val	Glu	Glu	Val	Thr	Gln	Asn	465	470	475	480
Asn	Phe	Arg	Leu	Leu	Phe	Lys	Gly	Ser	Glu	Met	Val	Val	Ala	Gly	Lys	485	490	495	
Leu	Gln	Asp	Arg	Gly	Pro	Asp	Val	Leu	Thr	Ala	Thr	Val	Ser	Gly	Lys	500	505	510	
Leu	Pro	Thr	Gln	Asn	Ile	Thr	Phe	Gln	Thr	Glu	Ser	Ser	Val	Ala	Glu	515	520	525	

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Gln Glu Ala Glu Phe Gln Ser Pro Lys Tyr Ile Phe His Asn Phe Met
 530 535 540
 Glu Arg Leu Trp Ala Tyr Leu Thr Ile Gln Gln Leu Leu Glu Gln Thr
 545 550 555 560
 Val Ser Ala Ser Asp Ala Asp Gln Gln Ala Leu Arg Asn Gln Ala Leu
 565 570 575
 Asn Leu Ser Leu Ala Tyr Ser Phe Val Thr Pro Leu Thr Ser Met Val
 580 585 590
 Val Thr Lys Pro Asp Asp Gln Glu Gln Ser Gln Val Ala Glu Lys Pro
 595 600 605
 Met Glu Gly Glu Ser Arg Asn Arg Asn Val His Ser Gly Ser Thr Phe
 610 615 620
 Phe Lys Tyr Tyr Leu Gln Gly Ala Lys Ile Pro Lys Pro Glu Ala Ser
 625 630 635 640
 Phe Ser Pro Arg Arg Gly Trp Asn Arg Gln Ala Gly Ala Ala Gly Ser
 645 650 655
 Arg Met Asn Phe Arg Pro Gly Val Leu Ser Ser Arg Gln Leu Gly Leu
 660 665 670
 Pro Gly Pro Pro Asp Val Pro Asp His Ala Ala Tyr His Pro Phe Arg
 675 680 685
 Arg Leu Ala Ile Leu Pro Ala Ser Ala Pro Pro Ala Thr Ser Asn Pro
 690 695 700
 Asp Pro Ala Val Ser Arg Val Met Asn Met Lys Ile Glu Glu Thr Thr
 705 710 715 720
 Met Thr Thr Gln Thr Pro Ala Pro Ile Gln Ala Pro Ser Ala Ile Leu
 725 730 735
 Pro Leu Pro Gly Gln Ser Val Glu Arg Leu Cys Val Asp Pro Arg His
 740 745 750
 Arg Gln Gly Pro Val Asn Leu Leu Ser Asp Pro Glu Gln Gly Val Glu
 755 760 765
 Val Thr Gly Gln Tyr Glu Arg Glu Lys Ala Gly Phe Ser Trp Ile Glu
 770 775 780
 Val Thr Phe Lys Asn Pro Leu Val Trp Val His Ala Ser Pro Glu His
 785 790 795 800
 Val Val Val Thr Arg Asn Arg Arg Ser Ser Ala Tyr Lys Trp Lys Glu
 805 810 815
 Thr Leu Phe Ser Val Met Pro Gly Leu Lys Met Thr Met Asp Lys Thr
 820 825 830

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Gly Leu Leu Leu Leu Ser Asp Pro Asp Lys Val Thr Ile Gly Leu Leu
 835 840 845
 Phe Trp Asp Gly Arg Gly Glu Gly Leu Arg Leu Leu Leu Arg Asp Thr
 850 855 860
 Asp Arg Phe Ser Ser His Val Gly Gly Thr Leu Gly Gln Phe Tyr Gln
 865 870 875 880
 Glu Val Leu Trp Gly Ser Pro Ala Ala Ser Asp Asp Gly Arg Arg Thr
 885 890 895
 Leu Arg Val Gln Gly Asn Asp His Ser Ala Thr Arg Glu Arg Arg Leu
 900 905 910
 Asp Tyr Gln Glu Gly Pro Pro Gly Val Glu Ile Ser Cys Trp Ser Val
 915 920 925
 Glu Leu
 930

<210> 127
 <211> 191
 <212> PRT
 <213> Homo sapiens

<400> 127
 Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu
 1 5 10 15
 Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly
 20 25 30
 Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln
 35 40 45
 Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu
 50 55 60
 Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu
 65 70 75 80
 Met Arg Cys Gly Gly Cys Ser Asn Asp Glu Gly Leu Glu Cys Val Pro
 85 90 95
 Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His
 100 105 110
 Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys
 115 120 125
 Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly
 130 135 140
 Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr
 145 150 155 160

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Cys Lys Cys Ser Cys Lys Asn Thr His Ser Arg Cys Lys Ala Arg Gln
 165 170 175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg
 180 185 190

<210> 128

<211> 221

<212> PRT

<213> Homo sapiens

<400> 128

Met Pro Val Met Arg Leu Phe Pro Cys Phe Leu Gln Leu Leu Ala Gly
 1 5 10 15

Leu Ala Leu Pro Ala Val Pro Pro Gln Gln Trp Ala Leu Ser Ala Gly
 20 25 30

Asn Gly Ser Ser Glu Val Glu Val Val Pro Phe Gln Glu Val Trp Gly
 35 40 45

Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu
 50 55 60

Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu
 65 70 75 80

Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro
 85 90 95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly
 100 105 110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys
 115 120 125

Glu Cys Arg His Ser Pro Gly Arg Gln Ser Pro Asp Met Pro Gly Asp
 130 135 140

Phe Arg Ala Asp Ala Pro Ser Phe Leu Pro Pro Arg Arg Ser Leu Pro
 145 150 155 160

Met Leu Phe Arg Met Glu Trp Gly Cys Ala Leu Thr Gly Ser Gln Ser
 165 170 175

Ala Val Trp Pro Ser Ser Pro Val Pro Glu Glu Ile Pro Arg Met His
 180 185 190

Pro Gly Arg Asn Gly Lys Lys Gln Gln Arg Lys Pro Leu Arg Glu Lys
 195 200 205

Met Lys Pro Glu Arg Cys Gly Asp Ala Val Pro Arg Arg
 210 215 220

<210> 129

<211> 1356

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<212> PRT

<213> Homo sapiens

<400> 129

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Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
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Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
          20          25          30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
          35          40          45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
          50          55          60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
 65          70          75          80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
          85          90          95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
          100          105          110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
          115          120          125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
          130          135          140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
          145          150          155          160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
          165          170          175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
          180          185          190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
          195          200          205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
          210          215          220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
          225          230          235          240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
          245          250          255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
          260          265          270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
          275          280          285

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Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
 290 295 300
 Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
 305 310 315 320
 Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met
 325 330 335
 Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala
 340 345 350
 Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly
 355 360 365
 Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr
 370 375 380
 Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu
 385 390 395 400
 Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val
 405 410 415
 Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val
 420 425 430
 Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr
 435 440 445
 Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu
 450 455 460
 Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr
 465 470 475 480
 Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys
 485 490 495
 Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys
 500 505 510
 Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr
 515 520 525
 Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser
 530 535 540
 Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln
 545 550 555 560
 Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser
 565 570 575
 Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro
 580 585 590

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Ile	His	Val	Gly	Glu	Leu	Pro	Thr	Pro	Val	Cys	Lys	Asn	Leu	Asp	Thr	595	600	605
Leu	Trp	Lys	Leu	Asn	Ala	Thr	Met	Phe	Ser	Asn	Ser	Thr	Asn	Asp	Ile	610	615	620
Leu	Ile	Met	Glu	Leu	Lys	Asn	Ala	Ser	Leu	Gln	Asp	Gln	Gly	Asp	Tyr	625	630	635
Val	Cys	Leu	Ala	Gln	Asp	Arg	Lys	Thr	Lys	Lys	Arg	His	Cys	Val	Val	645	650	655
Arg	Gln	Leu	Thr	Val	Leu	Glu	Arg	Val	Ala	Pro	Thr	Ile	Thr	Gly	Asn	660	665	670
Leu	Glu	Asn	Gln	Thr	Thr	Ser	Ile	Gly	Glu	Ser	Ile	Glu	Val	Ser	Cys	675	680	685
Thr	Ala	Ser	Gly	Asn	Pro	Pro	Pro	Gln	Ile	Met	Trp	Phe	Lys	Asp	Asn	690	695	700
Glu	Thr	Leu	Val	Glu	Asp	Ser	Gly	Ile	Val	Leu	Lys	Asp	Gly	Asn	Arg	705	710	715
Asn	Leu	Thr	Ile	Arg	Arg	Val	Arg	Lys	Glu	Asp	Glu	Gly	Leu	Tyr	Thr	725	730	735
Cys	Gln	Ala	Cys	Ser	Val	Leu	Gly	Cys	Ala	Lys	Val	Glu	Ala	Phe	Phe	740	745	750
Ile	Ile	Glu	Gly	Ala	Gln	Glu	Lys	Thr	Asn	Leu	Glu	Ile	Ile	Ile	Leu	755	760	765
Val	Gly	Thr	Ala	Val	Ile	Ala	Met	Phe	Phe	Trp	Leu	Leu	Leu	Val	Ile	770	775	780
Ile	Leu	Arg	Thr	Val	Lys	Arg	Ala	Asn	Gly	Gly	Glu	Leu	Lys	Thr	Gly	785	790	795
Tyr	Leu	Ser	Ile	Val	Met	Asp	Pro	Asp	Glu	Leu	Pro	Leu	Asp	Glu	His	805	810	815
Cys	Glu	Arg	Leu	Pro	Tyr	Asp	Ala	Ser	Lys	Trp	Glu	Phe	Pro	Arg	Asp	820	825	830
Arg	Leu	Lys	Leu	Gly	Lys	Pro	Leu	Gly	Arg	Gly	Ala	Phe	Gly	Gln	Val	835	840	845
Ile	Glu	Ala	Asp	Ala	Phe	Gly	Ile	Asp	Lys	Thr	Ala	Thr	Cys	Arg	Thr	850	855	860
Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Gly	Ala	Thr	His	Ser	Glu	His	Arg	865	870	875
Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	His	His	Leu	885	890	895

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Asn	Val	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gly	Gly	Pro	Leu
			900					905					910		
Met	Val	Ile	Val	Glu	Phe	Cys	Lys	Phe	Gly	Asn	Leu	Ser	Thr	Tyr	Leu
		915					920					925			
Arg	Ser	Lys	Arg	Asn	Glu	Phe	Val	Pro	Tyr	Lys	Thr	Lys	Gly	Ala	Arg
	930					935					940				
Phe	Arg	Gln	Gly	Lys	Asp	Tyr	Val	Gly	Ala	Ile	Pro	Val	Asp	Leu	Lys
945					950					955					960
Arg	Arg	Leu	Asp	Ser	Ile	Thr	Ser	Ser	Gln	Ser	Ser	Ala	Ser	Ser	Gly
				965					970					975	
Phe	Val	Glu	Glu	Lys	Ser	Leu	Ser	Asp	Val	Glu	Glu	Glu	Glu	Ala	Pro
			980					985					990		
Glu	Asp	Leu	Tyr	Lys	Asp	Phe	Leu	Thr	Leu	Glu	His	Leu	Ile	Cys	Tyr
	995						1000					1005			
Ser	Phe	Gln	Val	Ala	Lys	Gly	Met	Glu	Phe	Leu	Ala	Ser	Arg	Lys	Cys
	1010					1015					1020				
Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Leu	Ser	Glu	Lys	Asn
1025				1030					1035						1040
Val	Val	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Tyr	Lys	Asp
			1045					1050					1055		
Pro	Asp	Tyr	Val	Arg	Lys	Gly	Asp	Ala	Arg	Leu	Pro	Leu	Lys	Trp	Met
		1060					1065						1070		
Ala	Pro	Glu	Thr	Ile	Phe	Asp	Arg	Val	Tyr	Thr	Ile	Gln	Ser	Asp	Val
	1075					1080					1085				
Trp	Ser	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Phe	Ser	Leu	Gly	Ala	Ser
	1090				1095					1100					
Pro	Tyr	Pro	Gly	Val	Lys	Ile	Asp	Glu	Glu	Phe	Cys	Arg	Arg	Leu	Lys
1105				1110					1115						1120
Glu	Gly	Thr	Arg	Met	Arg	Ala	Pro	Asp	Tyr	Thr	Thr	Pro	Glu	Met	Tyr
			1125					1130					1135		
Gln	Thr	Met	Leu	Asp	Cys	Trp	His	Gly	Glu	Pro	Ser	Gln	Arg	Pro	Thr
		1140					1145					1150			
Phe	Ser	Glu	Leu	Val	Glu	His	Leu	Gly	Asn	Leu	Leu	Gln	Ala	Asn	Ala
	1155					1160						1165			
Gln	Gln	Asp	Gly	Lys	Asp	Tyr	Ile	Val	Leu	Pro	Ile	Ser	Glu	Thr	Leu
1170					1175					1180					
Ser	Met	Glu	Glu	Asp	Ser	Gly	Leu	Ser	Leu	Pro	Thr	Ser	Pro	Val	Ser
1185				1190					1195						1200

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Cys Met Glu Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn
 1205 1210 1215
 Thr Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
 1220 1225 1230
 Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu
 1235 1240 1245
 Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val Leu
 1250 1255 1260
 Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu Ser Pro
 1265 1270 1275 1280
 Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser Val Ala Ser
 1285 1290 1295
 Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser Gly Tyr His Ser Asp
 1300 1305 1310
 Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu Ala Glu Leu Leu Lys
 1315 1320 1325
 Leu Ile Glu Ile Gly Val Gln Thr Gly Ser Thr Ala Gln Ile Leu Gln
 1330 1335 1340
 Pro Asp Ser Gly Thr Thr Leu Ser Ser Pro Pro Val
 1345 1350 1355

<210> 130
 <211> 98
 <212> PRT
 <213> Homo sapiens

<400> 130
 Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
 1 5 10 15
 Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
 20 25 30
 Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
 35 40 45
 Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
 50 55 60
 Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
 65 70 75 80
 Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg
 85 90 95

Ser Pro

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<210> 131
 <211> 94
 <212> PRT
 <213> Homo sapiens

<400> 131
 Met Ser Val Lys Gly Met Ala Ile Ala Leu Ala Val Ile Leu Cys Ala
 1 5 10 15
 Thr Val Val Gln Gly Phe Pro Met Phe Lys Arg Gly Arg Cys Leu Cys
 20 25 30
 Ile Gly Pro Gly Val Lys Ala Val Lys Val Ala Asp Ile Glu Lys Ala
 35 40 45
 Ser Ile Met Tyr Pro Ser Asn Asn Cys Asp Lys Ile Glu Val Ile Ile
 50 55 60
 Thr Leu Lys Glu Asn Lys Gly Gln Arg Cys Leu Asn Pro Lys Ser Lys
 65 70 75 80
 Gln Ala Arg Leu Ile Ile Lys Lys Val Glu Arg Lys Asn Phe
 85 90

<210> 132
 <211> 5102
 <212> DNA
 <213> Homo sapiens

<400> 132
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 tgataatgca cgaggaggggc gaggtggacg gcaaagccat tcctgacctc accgcgccccg 180
 tggccgcgct gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa 240
 ccactgagga tcagattttg aagagagata tgccaccagc atttattaag gttgagaatg 300
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ctctaaaaga	tccttttttaa	attcagtcct	aagaaagagg	agtgtctgtc	ccctaagagt	4380
gtttaatggc	aaggcagccc	tgtctgaagg	acacttctg	cctaaggagg	agtggatatt	4440
gcagactaga	attctagtgc	tgctgaagat	gaatcaatgg	gaaatactac	tcctgtaatt	4500
cctacctccc	tgcaaccaac	tacaaccaag	ctctctgcat	ctactcccaa	gtatgggggt	4560
caagagagta	atgggtttca	tatttcttat	caccacagta	agttcctact	aggcaaaatg	4620
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<213> Homo sapiens

<400> 137

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<400> 141

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<210> 142

<211> 1137

<212> DNA

<213> Homo sapiens

<400> 142

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<210> 143

<211> 1270

<212> DNA

<213> Homo sapiens

118/147

<400> 143

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<211> 3953

<212> DNA

<213> Homo sapiens

<400> 144

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119/147

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<210> 145

<211> 3213

<212> DNA

<213> Homo sapiens

<400> 145

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120/147

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<210> 146

<211> 2602

<212> DNA

<213> Homo sapiens

<400> 146

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121/147

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125/147

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<212> DNA

<213> Homo sapiens

<400> 154

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

<400> 156

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<210> 157

<211> 1611

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<212> DNA

<213> Homo sapiens

<400> 157

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tgtggtcaga agagaggggg caagcagaaa agcagaggaa caaatttgga ggctaaaata 180
acattctaca taaggaacta tactacagta gaattaattg atagcaggga ttaagagatg 240
taaatagaatt tgagatacat attctagagg tagaatgtgc aatactTTTT gtatgtccat 300
atacagaaat tggttgcatt ttctttaaataaaaaagattt tttaaaagtc agtgagctgt 360
tatgttttct tccctctgac ttcaattcct tttgtttgag agaagttggc atgctgtcaa 420
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ctgaaacctg gatacagatt gtttgctaag agacaacat ggtcaataaa atgtatatatt 1560
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<210> 158

<211> 155

<212> DNA

<213> Homo sapiens

<400> 158

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aagtcaatgt ttttaagatt ctattactct cttca 155

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<210> 159

<211> 312

<212> DNA

<213> Homo sapiens

<400> 159

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gcttactgtc tgccttgaga acttatgaac catatggatc cctggttcaa caaatacgaa 120
ttctctcctt gggctcaatt ggagctccca agtccagctt tttcaactca gtgaggtctg 180
ttttccaagg gcatgtaacg catcaggctt tgggtgggcac taatacaact gggatatctg 240
agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaat caattatatt 300
tcaaaagctt tt 312

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136/147

<210> 160
 <211> 447
 <212> DNA
 <213> Homo sapiens

<400> 160
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 caacttttatt acatatagac ttcatctcaa ttataataa aaaatgaatc tttaaaattg 120
 cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac 180
 ctgccgttta ttctgtgtga ctcaactggg ctgagtgaga aagaaggcgg cctgtgcagg 240
 gatgacatat tctatatctt gaacggtaac attcgtgata gataccagg taaatatttgac 300
 taatgagaaa ttataactga tttttaaaat gcttattttt gtacaaatgt atcagcgttt 360
 atcttcttaa attatacttg ctcaagatcc tttgtctctt ttagattttt tttttcaaaa 420
 agaataaaaa catctcgagg gctcttc 447

<210> 161
 <211> 341
 <212> DNA
 <213> Homo sapiens

<400> 161
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 cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac 120
 agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctctctcag 180
 atgatagtaa agatcaaaaag aattcaaagg gagttggtaa acgctggtga gtctcattcc 240
 actttgctaa gggtaatacc actaagggtta attgactaga ctgtatttta gaatgctttt 300
 tggacaggat aaagaactta agtcattgca tatttcaatc t 341

<210> 162
 <211> 288
 <212> DNA
 <213> Homo sapiens

<400> 162
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 acttgaaaaa actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg 120
 tacatgtggc ttgctcact catgtggata gcatggattt gattacaaaa ggtgacctta 180
 tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc cttcgtaaac 240
 acattttctg gggatatgta ctacaatcac atactagtgt gtataaaa 288

<210> 163
 <211> 372
 <212> DNA
 <213> Homo sapiens

<400> 163
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 ctagagggaag tccaaagaaa acttggaatt gctctttctg acatctcggg ggtagcaat 180
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 cgaatgctat gggctgcaga tgacttctta gaggatttgc cttttgagca aataggtaga 300
 tggtttggtg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttggtac 360
 tattaataac tg 372

137/147

<210> 164
 <211> 483
 <212> DNA
 <213> Homo sapiens

<400> 164
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 aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaagggttc 120
 acgtaaatth cctcacatca cagaagatta aaattcagaa aggagaaaac acagacccaaa 180
 gagaagtatc taagacccaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata 240
 gaacattgta gtacttgtaa ataactagaa ataacatgat ttagtcataa ttgtgaaaaa 300
 taataataat ttttcttgga tttatgttct gtatctgtga aaaaataaat ttcttataaa 360
 actcgggtct aacttgagag tgtgtgtgat tttggaaaaa ttatgatttg tcagcatctt 420
 ctgatattca ctgctttcat cttaattttg ccttctgatt ttatttctaa agtatgtgat 480
 ttt 483

<210> 165
 <211> 25
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Primer

<400> 165
 gctctcttat ttgtaccggt ttttg 25

<210> 166
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Primer

<400> 166
 aagctagtga ctgtcaccga tcag 24

<210> 167
 <211> 16
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Probe

<400> 167
 tcatgtttcc aatctc 16

<210> 168
 <211> 30
 <212> DNA
 <213> Artificial Sequence

138/147

<220>
<223> Description of Artificial Sequence: Primer

<400> 168
cctgatataa atgcaatatt aatgccttta 30

<210> 169
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 169
aagaaccggg agagcaaaca t 21

<210> 170
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 170
atctatgcc aagatcactt 20

<210> 171
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 171
ggagcaccgc ctgtgaa 17

<210> 172
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 172
tgtgcgttgc ctgaatgaac 20

<210> 173
<211> 16

139/147

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 173
accaacctga agacac 16

<210> 174
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 174
tctcgactga atggactttg ca 22

<210> 175
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 175
ttgtgtaccc cgcaccaa 18

<210> 176
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 176
cacacctcta tcccggc 17

<210> 177
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 177
gctgcatgtg gatcctgaga 20

140/147

<210> 178
 <211> 25
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Primer

<400> 178
 tgagtagcca gaataatcac catca 25

<210> 179
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Probe

<400> 179
 cttcaagctc ctgggtaa 18

<210> 180
 <211> 136
 <212> DNA
 <213> Homo sapiens

<400> 180
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 ctaaataaac atgtgc 136

<210> 181
 <211> 1066
 <212> PRT
 <213> Homo sapiens

<400> 181
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 1 5 10 15
 Ala Gln Gln Ile Ser His Leu Val Ile Met His Glu Glu Gly Glu Val
 20 25 30
 Asp Gly Lys Ala Ile Pro Asp Leu Thr Ala Pro Val Ala Ala Val Gln
 35 40 45
 Ala Ala Val Ser Asn Leu Val Arg Val Gly Lys Glu Thr Val Gln Thr
 50 55 60
 Thr Glu Asp Gln Ile Leu Lys Arg Asp Met Pro Pro Ala Phe Ile Lys
 65 70 75 80
 Val Glu Asn Ala Cys Thr Lys Leu Val Gln Ala Ala Gln Met Leu Gln
 85 90 95

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Ser Asp Pro Tyr Ser Val Pro Ala Arg Asp Tyr Leu Ile Asp Gly Ser
 100 105 110
 Arg Gly Ile Leu Ser Gly Thr Ser Asp Leu Leu Leu Thr Phe Asp Glu
 115 120 125
 Ala Glu Val Arg Lys Ile Ile Arg Val Cys Lys Gly Ile Leu Glu Tyr
 130 135 140
 Leu Thr Val Ala Glu Val Val Glu Thr Met Glu Asp Leu Val Thr Tyr
 145 150 155 160
 Thr Lys Asn Leu Gly Pro Gly Met Thr Lys Met Ala Lys Met Ile Asp
 165 170 175
 Glu Arg Gln Gln Glu Leu Thr His Gln Glu His Arg Val Met Leu Val
 180 185 190
 Asn Ser Met Asn Thr Val Lys Glu Leu Leu Pro Val Leu Ile Ser Ala
 195 200 205
 Met Lys Ile Phe Val Thr Thr Lys Asn Ser Lys Asn Gln Gly Ile Glu
 210 215 220
 Glu Ala Leu Lys Asn Arg Asn Phe Thr Val Glu Lys Met Ser Ala Glu
 225 230 235 240
 Ile Asn Glu Ile Ile Arg Val Leu Gln Leu Thr Ser Trp Asp Glu Asp
 245 250 255
 Ala Trp Ala Ser Lys Asp Thr Glu Ala Met Lys Arg Ala Leu Ala Ser
 260 265 270
 Ile Asp Ser Lys Leu Asn Gln Ala Lys Gly Trp Leu Arg Asp Pro Ser
 275 280 285
 Ala Ser Pro Gly Asp Ala Gly Glu Gln Ala Ile Arg Gln Ile Leu Asp
 290 295 300
 Glu Ala Gly Lys Val Gly Glu Leu Cys Ala Gly Lys Glu Arg Arg Glu
 305 310 315 320
 Ile Leu Gly Thr Cys Lys Met Leu Gly Gln Met Thr Asp Gln Val Ala
 325 330 335
 Asp Leu Arg Ala Arg Gly Gln Gly Ser Ser Pro Val Ala Met Gln Lys
 340 345 350
 Ala Gln Gln Val Ser Gln Gly Leu Asp Val Leu Thr Ala Lys Val Glu
 355 360 365
 Asn Ala Ala Arg Lys Leu Glu Ala Met Thr Asn Ser Lys Gln Ser Ile
 370 375 380
 Ala Lys Lys Ile Asp Ala Ala Gln Asn Trp Leu Ala Asp Pro Asn Gly
 385 390 395 400

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Gly Pro Glu Gly Glu Glu Gln Ile Arg Gly Ala Leu Ala Glu Ala Arg
 405 410 415
 Lys Ile Ala Glu Leu Cys Asp Asp Pro Lys Glu Arg Asp Asp Ile Leu
 420 425 430
 Arg Ser Leu Gly Glu Ile Ser Ala Leu Thr Ser Lys Leu Ala Asp Leu
 435 440 445
 Arg Arg Gln Gly Lys Gly Asp Ser Pro Glu Ala Arg Ala Leu Ala Lys
 450 455 460
 Gln Val Ala Thr Ala Leu Gln Asn Leu Gln Thr Lys Thr Asn Arg Ala
 465 470 475 480
 Val Ala Asn Ser Arg Pro Ala Lys Ala Val His Leu Glu Gly Lys
 485 490 495
 Ile Glu Gln Ala Gln Arg Trp Ile Asp Asn Pro Thr Val Asp Asp Arg
 500 505 510
 Gly Val Gly Gln Ala Ala Ile Arg Gly Leu Val Ala Glu Gly His Arg
 515 520 525
 Leu Ala Asn Val Met Met Gly Pro Tyr Arg Gln Asp Leu Leu Ala Lys
 530 535 540
 Cys Asp Arg Val Asp Gln Leu Thr Ala Gln Leu Ala Asp Leu Ala Ala
 545 550 555 560
 Arg Gly Glu Gly Glu Ser Pro Gln Ala Arg Ala Leu Ala Ser Gln Leu
 565 570 575
 Gln Asp Ser Leu Lys Asp Leu Lys Ala Arg Met Gln Glu Ala Met Thr
 580 585 590
 Gln Glu Val Ser Asp Val Phe Ser Asp Thr Thr Thr Pro Ile Lys Leu
 595 600 605
 Leu Ala Val Ala Ala Thr Ala Pro Pro Asp Ala Pro Asn Arg Glu Glu
 610 615 620
 Val Phe Asp Glu Arg Ala Ala Asn Phe Glu Asn His Ser Gly Lys Leu
 625 630 635 640
 Gly Ala Thr Ala Glu Lys Ala Ala Ala Val Gly Thr Ala Asn Lys Ser
 645 650 655
 Thr Val Glu Gly Ile Gln Ala Ser Val Lys Thr Ala Arg Glu Leu Thr
 660 665 670
 Pro Gln Val Val Ser Ala Ala Arg Ile Leu Leu Arg Asn Pro Gly Asn
 675 680 685
 Gln Ala Ala Tyr Glu His Phe Glu Thr Met Lys Asn Gln Trp Ile Asp
 690 695 700

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Asn	Val	Glu	Lys	Met	Thr	Gly	Leu	Val	Asp	Glu	Ala	Ile	Asp	Thr	Lys	705	710	715	720
Ser	Leu	Leu	Asp	Ala	Ser	Glu	Glu	Ala	Ile	Lys	Lys	Asp	Leu	Asp	Lys	725	730	735	
Cys	Lys	Val	Ala	Met	Ala	Asn	Ile	Gln	Pro	Gln	Met	Leu	Val	Ala	Gly	740	745	750	
Ala	Thr	Ser	Ile	Ala	Arg	Arg	Ala	Asn	Arg	Ile	Leu	Leu	Val	Ala	Lys	755	760	765	
Arg	Glu	Val	Glu	Asn	Ser	Glu	Asp	Pro	Lys	Phe	Arg	Glu	Ala	Val	Lys	770	775	780	
Ala	Ala	Ser	Asp	Glu	Leu	Ser	Lys	Thr	Ile	Ser	Pro	Met	Val	Met	Asp	785	790	795	800
Ala	Lys	Ala	Val	Ala	Gly	Asn	Ile	Ser	Asp	Pro	Gly	Leu	Gln	Lys	Ser	805	810		815
Phe	Leu	Asp	Ser	Gly	Tyr	Arg	Ile	Leu	Gly	Ala	Val	Ala	Lys	Val	Arg	820	825		830
Glu	Ala	Phe	Gln	Pro	Gln	Glu	Pro	Asp	Phe	Pro	Pro	Pro	Pro	Pro	Asp	835	840		845
Leu	Glu	Gln	Leu	Arg	Leu	Thr	Asp	Glu	Leu	Ala	Pro	Pro	Lys	Pro	Pro	850	855	860	
Leu	Pro	Glu	Gly	Glu	Val	Pro	Pro	Pro	Arg	Pro	Pro	Pro	Pro	Glu	Glu	865	870	875	880
Lys	Asp	Glu	Glu	Phe	Pro	Glu	Gln	Lys	Ala	Gly	Glu	Val	Ile	Asn	Gln	885	890		895
Pro	Met	Met	Met	Ala	Ala	Arg	Gln	Leu	His	Asp	Glu	Ala	Arg	Lys	Trp	900	905		910
Ser	Ser	Lys	Gly	Asn	Asp	Ile	Ile	Ala	Ala	Ala	Lys	Arg	Met	Ala	Leu	915	920		925
Leu	Met	Ala	Glu	Met	Ser	Arg	Leu	Val	Arg	Gly	Gly	Ser	Gly	Thr	Lys	930	935	940	
Arg	Ala	Leu	Ile	Gln	Cys	Ala	Lys	Asp	Ile	Ala	Lys	Ala	Ser	Asp	Glu	945	950	955	960
Val	Thr	Arg	Leu	Ala	Lys	Glu	Val	Ala	Lys	Gln	Cys	Thr	Asp	Lys	Arg	965	970		975
Ile	Arg	Thr	Asn	Leu	Leu	Gln	Val	Cys	Glu	Arg	Ile	Pro	Thr	Ile	Ser	980	985		990
Thr	Gln	Leu	Lys	Ile	Leu	Ser	Thr	Val	Lys	Ala	Thr	Met	Leu	Gly	Arg	995	1000	1005	

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Thr Asn Ile Ser Asp Glu Glu Ser Glu Gln Ala Thr Glu Met Leu Val
 1010 1015 1020

His Asn Ala Gln Asn Leu Met Gln Ser Val Lys Glu Thr Val Arg Glu
 1025 1030 1035 1040

Ala Glu Ala Ala Ser Ile Lys Ile Arg Thr Asp Ala Gly Phe Thr Leu
 1045 1050 1055

Arg Trp Val Arg Lys Thr Pro Trp Tyr Gln
 1060 1065

<210> 182

<211> 1666

<212> DNA

<213> Homo sapiens

<400> 182

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<210> 183

<211> 99

<212> PRT

<213> Homo sapiens

<400> 183

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<210> 185

<211> 224

<212> PRT

<213> Homo sapiens

<400> 185

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Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
      35              40              45

Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
      50              55              60

Arg Gly Tyr Ser Ile Phe Ser Tyr Ala Thr Lys Arg Gln Asp Asn Glu
      65              70              75              80

Ile Leu Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
      85              90              95

Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
      100             105             110

His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
      115             120             125

Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Lys Gly Tyr Thr
      130             135             140

Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe
      145             150             155             160

Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu Val Gly Asp Ile Gly Asn
      165             170             175

Val Asn Met Trp Asp Phe Val Leu Ser Pro Asp Glu Ile Asn Thr Ile
      180             185             190

Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val Leu Asn Trp Arg Ala Leu
      195             200             205

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Lys	Tyr	Glu	Val	Gln	Gly	Glu	Val	Phe	Thr	Lys	Pro	Gln	Leu	Trp	Pro
210						215					220				